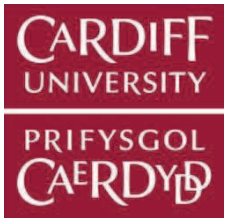

The prevalence of urinary tract infection (UTI) in children under five years old presenting with an acute illness in UK general practice

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Summary of thesis

Urinary tract infections (UTI) in young children have been associated with serious long-term complications such as renal scarring, hypertension and renal failure. The presenting symptoms of UTI in children are non-specific. If UTI is not suspected, a urine sample is not obtained, and without this, UTI cannot be diagnosed. There is evidence that the diagnosis is often missed.

Most published studies have not systematically sampled urine, and those that have are largely based in US emergency departments and only include highly selected groups of children. The true prevalence of UTI in acutely ill children presenting in UK general practice is therefore unknown.

My thesis consists of a literature review discussing the association of childhood UTI with long-term complications, the challenges of diagnosis and the evidence that UTIs are being missed; a systematic review of papers reporting UTI prevalence in children which highlights the need for a study in UK general practice; a pilot study to determine the feasibility of recruiting children and obtaining urine samples in UK general practice; and a prospective cohort study to determine the point prevalence of UTI in 597 presenting children, determine the predictive value of presenting symptoms, signs and risk factors, and describe the clinical outcomes for children with UTI.

I found that the prevalence of UTI was 5.9% (95% confidence interval: 4.3-8.0%). This may be sufficiently high to justify increased urine sampling in general practice.

A multi-variable logistic regression model identified younger age range, pain on passing urine (dysuria) and urinary frequency as being associated with UTI. I propose a urine sampling strategy for GPs assessing acutely ill children and compare this to suspicion-led sampling and current guidelines. In my discussion I discuss the limitations, generalisability and implications of these findings.

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Glossary of terms and abbreviations

A&E	Accident and Emergency department
ASB	Asymptomatic bacteriuria
cfu/ml	colony forming units per millilitre of urine
CLED agar	Cystine-Lactose-Electrolyte-Deficient agar
CRF	Case report form
DMSA	Technetium^{99m} dimercaptosuccinic acid
E.coli	*Escherichia coli*
ED	Emergency department
EURICA	The epidemiology of urinary tract infections in children with acute illness presenting in primary care
GP	General Practitioner
HPA	Health Protection Agency
LRTI	Lower respiratory tract infection
MCUG	Micturating cystourethrogram
MSU	Mid-stream urine sample
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PCR	Polymerase chain reaction
R&D	Research and Development
SOP	Standard operating procedures
SPA	Supra-pubic aspiration
SPARC	Streamlined NHS permissions approach to research Cymru
SSI	Site specific information
URTI	Upper respiratory tract infection
USS	Ultrasound scan
UTI	Urinary tract infection

VUR	Vesico-ureteric reflux
WBC	White blood cells

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Chapter 1: Background

Introduction – Research aim

The main aim of this thesis is to determine the prevalence of urinary tract infection (UTI) in young children presenting with an acute illness in primary care.

In this chapter I will discuss why this is an important question, the difficulties of diagnosing UTI and some of the challenges for research studies attempting to address these issues. For each of these questions I conducted a thorough review of the literature. A systematic review of the existing literature concerning the prevalence of UTI in children is presented in chapter two.

Importance of the research question

Importance of UTI in children

The diagnosis and treatment of UTI in children has been considered to be particularly important due to both short term and long term sequelae.[1 2] UTI is one of the causes of serious bacterial illness in infants requiring hospital admission and has been associated with significant morbidity.[3] It has also been thought to cause, or contribute to, the development of renal scarring and later to renal failure, hypertension and pre-eclampsia. In this section I will discuss the evidence for the link with long-term complications.

Long term complications

Renal scarring following UTI

There is evidence that UTI leads to renal scarring in some cases.[1 4] Renal scarring is the term used to describe radiological evidence of persistent kidney damage.[5] Renal scarring is thought to occur as a result of pyelonephritis (infection involving the kidneys). Pyelonephritis causes acute damage to the kidneys which can be detected by Technetium^{99m} dimercaptosuccinic acid (DMSA) scans performed during or soon after a UTI.[6 7] The acute damage seen with pyelonephritis usually resolves. However, some children with abnormalities on an early scan will have persistent abnormalities on later scans. Persistent abnormalities are known as renal scarring. Renal scarring has been associated with long-term complications including renal failure, hypertension and pre-eclampsia.[1 8-10]

Shaikh et al. (2010) conducted a systematic review of the risk of renal scarring following a first UTI in childhood.[11] They included 33 studies with a total of 4891 children. Papers were only included if results of acute (≤15 days) or follow-up (>5 months) DMSA scans were presented and when the studies were based on a cohort of children with UTI all of whom were referred for DMSA scans. They found that 57% children had evidence of acute pyelonephritis on early scans. This was based on 29 studies and they commented that there was 'considerable variation across studies', with significant heterogeneity ($p<0.001$). Most children (85%) did not develop renal scars after UTI. The overall prevalence of renal scarring (i.e. abnormalities at the follow-up scan which are likely to be persistent) was 18% (95% CI 14-23). This was based on 14 studies and there was 'significant heterogeneity (test for heterogeneity $p<0.001$) in these studies'.

Age and renal scarring

It has been generally believed that younger children are more at risk of renal scarring, although a review in the National Institute for Health and Clinical Excellence (NICE) guidelines concludes that "the situation on new and progressive renal scarring is not clear. In general, as children get older their risk of developing new renal scars reduces".[1 12] Berg and Johansson found that renal scarring was more likely in children with a first UTI under 3 years old, although they did not use DMSA scanning which is now considered the gold standard.[13 14] Coulthard et al found that the scarring rate following referral for a first febrile UTI was similar regardless of the child's age, even for children older than five years old (n=324 children).[4] They suggest that this was probably due to previous but unrecognised UTI when the child was younger. The same authors followed up children with a normal DMSA scan following initial UTI to determine the risk of subsequent scar formation depending on the age of the child.[12] They found that the risk of developing a new renal scar over the age of four was extremely low.

Culture results and scarring

Evidence of acute pyelonephritis and renal scarring has been found in children with equivocal or negative urine cultures.[15] Kanellopoulos et al (2005) showed that low count UTI was more common in infants and young children and that children with low count UTI had a similar prevalence of pyelonephritis, urogenital malformations, and clinical and laboratory

findings.[16] Some studies have found that renal scarring is more common in children with non-*E.coli* UTIs.[17 18]

The role of vesico-ureteric reflux (VUR)

The risk of renal scarring with UTI has been strongly associated with VUR. VUR is the reflux of urine from the bladder into the ureters and/or the kidneys. It was previously thought that renal scarring only occurs in the presence of VUR, but it is now recognised that renal scarring can occur following UTI without VUR.[1 11 19]

VUR can be caused by a congenital abnormality of the ureterovesical junction (primary VUR) or can be caused by increased pressure in the bladder due to bladder dysfunction or outlet obstruction (secondary VUR). VUR is found in 30-40% children investigated for UTI.[20 21] The incidence of primary VUR in the general population is reported to be about 1-3% [1 22] although a more recent paper suggests that this is vastly underestimating the likely prevalence of VUR and that VUR is 'fairly common even in healthy children'.[21]

Coulthard (2008) reviewed the evidence for the association between VUR, UTI and renal scarring and stated that a 'strong association between childhood UTI, VUR and kidney scarring has been recognised for many years, but their relationship is inconsistent'.[19] The NICE guidelines include a review of the association between VUR and renal scarring and conclude that 'renal scarring is much more common in children with VUR, and almost universal in the most severe grades'.[1] The most recent review, by Shaikh et al., found that children with VUR were 1.5 times more likely to have acute changes on DMSA scan, and 2.6 times more likely to have renal scarring than those without VUR.[11] However, Coulthard, NICE and Shaikh have all recognised that renal scarring can occur without VUR.[1 11 19]

Venhola et al (2010) questioned the association between VUR and UTI and VUR and renal scarring, suggesting that VUR is a lot more prevalent than previously thought, and less important in the development of renal scarring.[21] They stated that 'diagnosing and treating VUR has not been shown to reduce UTI recurrences or renal scarring' and that 'a focus on prompt and correct diagnosis of UTI could result in better prevention of renal damage'.[21]

Can antibiotics reduce renal scarring?

Guidelines emphasise the importance of prompt antibiotic treatment of UTI.[1] This is mainly because it is believed that prompt treatment with antibiotics will reduce or prevent renal scarring.

There is evidence that a delay in treatment of an acute UTI is more likely to result in renal scarring.[23-28] However, in 2008, Hewitt et al found that early antibiotic treatment did not reduce subsequent scarring.[29]

A recent paper (2012) found that delay in treatment *was* associated with renal scarring in both the presence and absence of VUR but that renal scars occurred with shorter delays in treatment if VUR was present.[7]

Renal failure, pre-eclampsia, hypertension

Renal scarring has been associated with long-term complications including renal failure, hypertension and pre-eclampsia.[1 8-10] If renal scarring can be prevented by prompt treatment of childhood UTI, it is hoped that the serious long-term complications will also be prevented.

The evidence for the association between UTI, renal scarring and long term complications is weak.[1] In part, this is due to the long time between childhood UTI and the complications occurring; in part due to the low prevalence of the complications, and also due to the necessary design of studies which cannot show causation and are subject to bias, particularly attrition bias. Some researchers are now questioning these associations.[30 31]

Renal failure

Certainly, it is not clear how many children with UTI go on to develop end stage renal failure (ESRF) or other complications.[1 32] One estimate is that ESRF occurs in 0.01% of those with childhood UTI.[33] A more recent paper criticises this estimate, finding the risk of ESRF based on current data to be uncertain but at least between 0.03 and 0.1%, and probably significantly higher.[32]

Hypertension

NICE review the evidence for an association between UTI and hypertension.[1] They conclude that there may be a small risk of hypertension from UTI but that it is most likely if renal

scarring is severe. They comment that it is difficult to draw conclusions, largely because of the high prevalence of essential hypertension in the adult population.

Pre-eclampsia

There is very little evidence that UTI in childhood leads to pre-eclampsia in pregnancy. NICE found limited evidence that hypertension in pregnancy and pre-eclampsia were more likely if there was a history of childhood UTI and VUR.[1]

The NICE guidelines provide a comprehensive review of the risk of long term complications following UTI in childhood, and conclude that 'there are no appropriate studies that accurately estimate the risks of long term complications as a result of childhood UTI'.[1] They comment that 'a well designed cohort study investigating long-term outcomes including renal scarring and renal function of infants and children who have had UTI should be conducted in the UK'.

In the absence of such studies, the guidelines continue to advocate the early diagnosis and treatment of UTI in order to reduce the risk of any complications.[1]

Other complications

Recurrent UTI is common, and the risk seems to be highest for children presenting with UTI at younger ages, and is more common in girls than boys.[1 34] Merrick et al (1995) found that 78% of girls and 71% of boys presenting with UTI in the first year of life in the UK, experienced recurrence and 45% of girls and 39% of boys presenting aged over1 years experienced recurrence.[35]

Recurrence rates increase in girls as they get older, but not in boys.[1] A Dutch study in primary care found that 34% of children had at least one further episode of UTI in a 3 year period following an initial UTI.[36] There is also some evidence that children with UTI are more likely to have UTI as adults.[37]

Importance of knowing the prevalence

The importance of a condition not only depends on how serious it is, how ill the patient is likely to be or the possibility that it will cause complications in the future, but also on how common the condition is and the likelihood of it being the cause of a particular illness episode.

Children with UTI are difficult to diagnose as they often present with non-specific symptoms and signs which are also seen in many common childhood conditions.[2] General practitioners (GPs) frequently see ill children in their surgeries, most of whom have other more common conditions like upper respiratory tract infections. The majority of children are managed in the community by the GP. Infectious diseases account for about 40% consultations with ill children in the UK.[38] Non-specific symptoms are the main presentation in about 10% of consultations with children less than five years old.[39]

In order to identify the children who may have UTI and obtain a urine sample to diagnose the condition, GPs need to have a reasonably high degree of suspicion. If the prevalence of UTI among presenting ill children is sufficiently low, the level of suspicion will be low. If the prevalence of UTI is sufficiently high, then GPs should have a corresponding high level of suspicion, resulting in a higher chance of obtaining a urine sample, even without specific urinary symptom features.

The prevalence of UTI in the population of acutely ill presenting children corresponds to the 'pre-test probability', which is the probability that the child has a UTI before any further assessment of symptoms, signs or diagnostic testing is completed.

Current guidelines (published in 2007) recommend a high level of suspicion of UTI in young children and promote urine sampling in many more children than was previously recommended.[1] Without knowing the pre-test probability of UTI among presenting children, it will be difficult to convince GPs that it is appropriate to consider the diagnosis and change their current practice and request urine samples from many more children. In fact, if the prevalence is very low, this may not be an appropriate, cost effective strategy. If the prevalence is sufficiently high, there may be a case for obtaining and testing urine samples from all acutely ill children.

A study in 1983 questioned 200 paediatricians (academics and practitioners) in order to reach a consensus on the prevalence of UTI (yield) which would warrant sampling urine in all febrile infants.[40] All of the respondents agreed that a prevalence of 5% would warrant urine sampling in all febrile infants; and more than 80% felt that a prevalence of more than 3% would warrant urine sampling in all febrile infants. Approximately half felt that a prevalence of between 1 and 3% would warrant sampling urine from all febrile children. Table 1.1 is copied directly from their paper.

Table 1.1: Results table copied from Roberts et al [40]

Questionnaire responses

What yield is required to warrant urine culture in febrile infants?		
Yield (%)	**Academicians (%)**	**Practitioners (%)**
<1	10.4	11.7
1 to 3	67.5*	45.7*
3 to 5	92.2*	80*
>5	100*	100*

* Cumulative percentage

Missed diagnoses

The NICE guidelines published in 2007, note the difficulty of diagnosing UTI due to non-specific presenting symptoms and signs and because of the difficulty of urine collection.[1] The guidelines emphasise the importance of increasing urine sampling from ill children, particularly in primary care. Although the evidence that UTIs are being missed is not clearly stated, the guideline assumes that there is an under-diagnosis of UTI, with a paragraph entitled "Back to first steps: dealing with underdiagnosis of UTIs". In this short section they comment that, "there has been little evidence that the diagnosis of UTI in primary care in the UK has improved in pre-toilet-trained infants and children" [since the 1991 RCP guideline was published], referencing the three papers discussed below.[41-43] They note that Coulthard's study with increased education about UTI and urine sampling led to increases in the diagnosis of UTI.[1 43]

Coulthard et al report the results of a randomised controlled trial in UK general practice (n=88 practices).[43] Intervention practices had training on UTI in children, and were given management guidelines and direct access to a nurse practitioner who organised imaging and follow up with a nephrologist for children found to have positive culture. Direct access was only accepted if a urine sample was collected. They found that intervention practices referred twice as many children with confirmed UTI as control (normal practice) practices (6.42 vs. 3.45/1000 children/year). In infants under 1years old in intervention practices, there were four times more UTIs diagnosed and in children without specific urinary symptoms there were six times more UTIs diagnosed. This implies strongly that many UTIs are missed in primary care with standard practice. The authors felt that the education element of the intervention was of key importance.

This research was carried out in 2003 and since then, with the publication of the NICE guideline, there may be better awareness of the problem and possibly increased urine sampling behaviour amongst GPs.

A survey of 82 GPs in the UK concerning diagnosis and management of UTI in children (<2 years) found that only 14% stated that they would regularly send urine from febrile infants and toddlers.[41] Sixty three percent said that they sent urine in less than 10% of presenting children and 26% said that they never sent urine samples from children under two. The reasons given for these low figures for urine sampling were not that UTI was not suspected, but related to practical difficulties with urine collection and concerns of costs of investigation as well as a lack of awareness of the importance of UTI. Overall general difficulty or inability to obtain a urine sample was the most common reason given for being unable to exclude UTI.

Although this survey was carried out 15 years ago, many of the reasons given for low levels of urine sampling are still likely to apply. Certainly, the NICE guidelines published in 2007, still highlight these same issues as ongoing problems. This paper also highlights the point that even when guidelines have been published concerning UTI in children (the 1991 Royal College of Physicians guidelines had been published recommending all children with a fever of more than 38.5^{o}C without an obvious cause should have their urine sampled), this will not necessarily lead to a change in practice if it is still practically difficult.

Jadresic et al (1993) surveyed urine samples from children less than 15 years old from 53 general practices in the UK and found a ten-fold variation between general practices in the rate of urine sampling and rate of UTI in children.[42] They found that the number of urine specimens sent from a practice correlated very well with the number of samples with positive culture results; the more urine samples which were sent, the more UTIs were diagnosed. This could simply derive from increased numbers of coincidental asymptomatic bacteriuria being found, or false positive results due to contamination. However, these always could be the explanation for any positive culture results. It seems likely that if increased urine sampling detects more UTIs, then less urine sampling is probably leading to some cases being missed.

How often do GPs obtain urine samples?

Jadresic found that 2 urine samples were sent per 100 registered children aged less than two years old, per year.[42] We know that children under the age of five consult on average 6 times per year in primary care and approximately 87% of these consultations are for acute illness.[38] [44] [45] The results from Jadresic's study equate to urine being sampled in approximately 0.4% of illness consultations with children under age two.[42]

Based on these findings it seems likely that if a practice has a low rate of urine sampling, some UTIs will be missed.

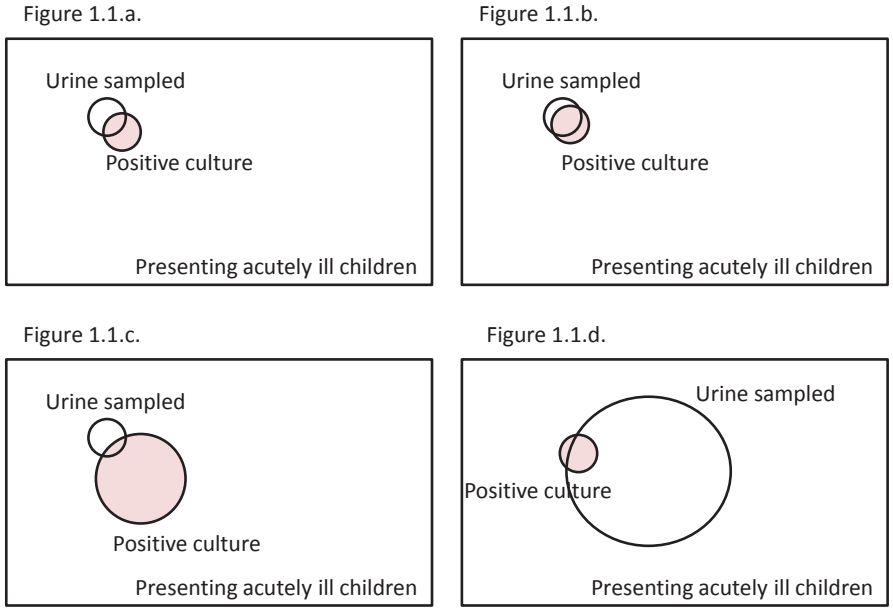
Another study of young children (aged under two) in Wales measured urine sampling rates from six general practices before and after an intervention designed to increase urine sampling and compared this with data from the remaining 47 (control) practices in the same area.[46] This showed a urine culture rate of approximately 30 per 1000 children per year in routine practice (control practices). This suggests that urine is sampled and sent for culture in approximately 0.6% of consultations in acutely unwell children (prior to the publication of the NICE guideline).

We do not know with adequate precision how many UTIs are being missed as we do not know the prevalence of UTI in presenting acutely ill children, and we do not know the prevalence because studies have not systematically sampled urine from all presenting ill children.

If urine is sampled in less than 1% consultations with acutely ill children, and if the prevalence of UTI among ill children is greater than 1%, then UTIs will be missed even if all of the urine samples sent are positive. For example, in 100 consultations with ill children, if the prevalence of UTI in this group is 1%, then one of these illness consultations would be a child with UTI. If urine is sampled in 1% of consultations with ill children, then the one urine sample taken in these 100 illness consultations would need to be aimed perfectly at the one child with UTI to identify it. Given that it is very difficult to predict UTI in young children from symptoms and signs, then such accurate targeting of testing would be unlikely. Increasing the proportion of urine sampling among ill children will increase the chance that that one UTI is correctly detected.

Figure 1.1 shows some possible urine sampling and positive culture scenarios. Figure 1.1.b represents low levels of urine sampling, with similar low levels of UTI prevalence (e.g. both 1%) with nearly all the UTIs being picked up by the urine sampling. Figure 1.1.a shows the more likely scenario where some UTIs are missed but with similarly low levels of both urine sampling and UTI. Of course, almost all of the UTIs could be missed with this sampling strategy. Figure 1.1.c represents low urine sampling (e.g. 1%) and higher levels of UTI prevalence (e.g. 3% -5%) and figure 1.1.d represents higher levels of urine sampling with low prevalence of UTI.

Figure 1.1: Possible urine sampling and positive culture scenarios



It is difficult to quantify how many are being missed as we do not know the prevalence of UTI in presenting ill children.

Jadesic found that in the under 2 year olds, 11% of the urine samples sent had positive culture results.[42] With such a small proportion of urine sampled, one would hope that or expect that the detection rate of UTI among those who did have their urine sampled would be much higher, and if nearing 100%, indicating that clinicians were correctly predicting the 1% of children with UTI with their sampling strategy. A prevalence of UTI of 11% detected in urine samples sent in less than 1% of illness consultations, would equate to a true prevalence of 0.1%.

From the studies in emergency departments which have designed studies with systematic sampling, the prevalence is much higher than 0.1%. So, despite not knowing the true prevalence of UTI in ill children presenting in primary care we can be fairly confident that there is a significant number of cases of UTI being missed.

If the true prevalence is 3% yet current practice is finding it to be 0.1% this implies that more than 90% of UTIs are being missed.

What can be done?

If symptoms or signs could be identified which were reliably predictive of UTI, the diagnostic process would be easier. Many papers have described the symptoms and signs of UTI in children and some of these are discussed below.

The most obvious solution would seem to be to increase urine sampling from acutely ill children in primary care. Coulthard and Jadresic both found that increased urine sampling was associated with increased numbers of UTIs detected.[42 43] However, Cunningham et al did not find that increasing urine sampling increased UTI detection at all.[46]

The NICE guidelines encourage a substantial increase in urine sampling, particularly from primary care. Although this is not explicitly stated, the guidelines (and table) advising when to obtain a urine sample in presenting ill children are very inclusive.[1]

Review of presenting symptoms and signs

The main problem with many of the papers describing presenting symptoms and signs of UTI is that urine is not systematically sampled from ill children. Therefore, the test to diagnose UTI is not performed in the majority of ill children and UTI is only diagnosed in those in whom the clinician suspected a UTI or chose to obtain and test a urine sample. Therefore, in these papers, the presenting symptoms and signs are only presenting symptoms and signs of *clinician suspected UTI*. For example, one recently published paper reports a large prospective cohort study of children under the age of five presenting to the ED in Australia (15 781 illness episodes).[47] Presenting symptoms and signs associated with serious bacterial illness including UTI are described. Unfortunately urine culture was only performed in 21% of children and so the prevalence of confirmed UTI of 3.2% is based only on those in whom UTI was suspected, therefore missing the presenting symptoms and signs of children with UTI who were not suspected of having UTI and who were unidentified.

Since we know that many UTIs are being missed in children in primary care [43] it is important to identify symptoms and signs in the group of children with UTI who are currently not suspected of having UTI, the very group these sort of studies would have missed.

We need to consider symptoms and signs of children from prospective studies which systematically sampled urine from all children. The problem with many of the studies which have systematically sampled urine is that the numbers with UTI are low or the symptoms and signs are not described. Many only include children with fever (see Chapter 2).

The NICE guidelines base their table of presenting symptoms and signs on thirteen studies.[1] Only one of these studies systematically sampled urine and this was only in febrile infants less than 2 months old with a rectal temperature of $\geq$38.3^{o}C. [48] I have summarised these studies in table 1.2 below.

Table 1.2: Characteristics of 13 studies described in NICE for presenting symptoms and signs

Study – first author & year	Setting	Number and age of participants	Diagnostic criteria of UTI	Systematic sampling?	Symptoms and signs
Winberg 1974 [28]	Children's hospital Sweden	Age under 16 596 cases of UTI Case series	Not stated	No	Fever (88%); failure to thrive uncommon.[Other symptoms reported in 5 separate papers]
Hallett 1976 [49]	GP UK	2-12 years 49 boys with definite infection. 51 controls Case control	MSU + dipslide culture by parents	No	2-5 yr old: Enuresis (50%), Dysuria/frequency (81%), haematuria (2%), Fever (8%), abdominal pain (6%), balanitis (4%). 6-12 yr olds: fever (29%), dysuria/frequency (82%), haematuria (29%), fever (18%), abdominal pain (39%), balanitis (21%)
Brooks 1977 [50]	GP UK	Age <15 years. 38 confirmed UTI, unknown denominator (not told how many presented/had urine cultured); 1632 children under 15 on GP list at the time and data collection for 4 years Case series	>100,000 orgs/ml from a dipslide culture of a clean catch specimen	No	Dysuria (71%), loin pain (8%), loin tenderness (5%), abdominal pain (32%), fever (21%), offensive urine (18%), night time wetting when previously dry (24%), daytime incontinence (5%), haematuria (3%)
Dickinson 1979 [51]	GP UK	Age under 15 156 children in who clinicians suspected UTI. 14 with UTI. Case series	>100,000 org/ml in 3 consecutive samples	No	Dysuria & frequency (43%), abdominal pain (21%), enuresis (14%), loin pain (7%), haematuria (7%), failure to thrive (7%)
Smellie 1981[52]	Hospital UK	744 children aged 0-12 years with confirmed UTI. Compared children with and without VUR Case control	Not stated	No	Fever (42%), abdominal or loin pain (31%), enuresis aged 5 or over (38%). Fever was more common in children with reflux.
Ginsburg 1982 [53]	Pediatric dept USA	Age 5 days- 8 months 100 cases UTI Case series	SPA in all. 96% >100,000 org/ml; 4% 40,000-80,000 org/ml	No	Fever (63%), irritable (55%), refused 1 or more feeds (38%), vomiting (36%), diarrhoea (31%), abdominal distension (8%), jaundice (7%),

Study – first author & year	Setting	Number and age of participants	Diagnostic criteria of UTI	Systematic sampling?	Symptoms and signs
Burbige 1984 [54]	Hospital USA	Age 2 weeks to 14 years 83 boys with UTI Case series		No	Fever (45%), Enuresis (8%), Haematuria (7%)
Smellie 1985 [55]	Hospital UK	120 children 2 weeks – 12 years who had had confirmed UTI and IVU Case series	Not stated	No	Fever (48%)* abdominal or loin pain (28%), chronic constipation (13%), uncoordinated voiding with residual urine (7%)
Messi 1989 [56]	Hospital Italy	Age under 14 223 with UTI Case series		No	Fever (65%) Dysuria and frequency (41%), Haematuria (11%), Failure to thrive (6%)
Hoberman 1993 [48]	ED Hospital USA	Febrile infants <1 year old Nested case control but systematically sampled 20 with UTI and 396 without UTI.	>10,000 cfu/ml from a catheter specimen	Infants < 2months- yes; infants >2 months No	Study only included febrile infants (temp >=38.3^{o}C) No statistical differences between the 2 groups. Those with UTI had vomiting (40%), diarrhoea (30%), irritability (80%), poor feeding (65%)
Craig 1998 [57]	ED at children's hospital Australia	Age under 5 304 cases UTI Case series	>10^{6} cfu/L on SPA or catheter or >10^{7} cfu/L from MSU or >10^{8}cfu/L + WBC>100 from bag	No	History of fever (80%), measure temp >37.5 (60%), irritable (52%), anorexia (49%), malaise/lethargy (44%), vomiting (42%), diarrhoea (21%), dysuria (15%), offensive urine (13%), abdominal pain (13%), 1st degree relative with PH UTI (11%), previous unexplained febrile episodes (11%), frequency (10%), increase in daytime wetting (7%), haematuria (7%), febrile convulsion (5%)
Honkinen 1999 [58]	Finland Hospital	1 week to 9.5 years 134 with bacteremic UTI. Compared to blood culture negative UTI so Case control		No	Fever (92%)**, irritablility (60%), vomiting (15%), Dysuria (1%), abdominal pain(7%), malaise (26%), poor feeding (20%)
Nayir 2001 [59]	Hospital Turkey	100 boys from 3 months – 10 years Case series	Urine culture but diagnostic value not stated	No	Fever <38.5^{o}C (48%), fever >38.5^{o}C (24%), vomiting and/or diarrhoea (22%), dysuria/frequency (34%), enuresis (7%), suprapubic discomfort (11%), abdominal pain (18%), flank pain (5%), malodorous urine (2%)

* there seems to be an error in the NICE guideline table which states that fever was present in 77% children in the Smellie 1985 study. On p1958 it states that 'the most common presenting symptoms were fever (57 children) and abdominal pain or loin pain (34).'57/120 =48%.

** NB these are children with positive culture AND positive blood cultures which may explain such a high proportion with fever.

For some reason, in the summary table presented in the NICE guideline, they have left out the studies by Winberg et al[28] and Hoberman et al.[48] Hoberman's study is the only one out of all of those discussed in the NICE guidelines which has attempted to systematically sample urine.

The following table (1.3) shows the presenting symptoms and signs from studies in which UTI was detected following *systematic* sampling of groups of presenting ill children. Unfortunately the majority of these studies do not give presenting symptoms and signs.

Table 1.3 Presenting symptoms and signs (if given) from papers describing studies which have used systematic urine sampling.

Lead author and date	Setting	Age and sample size	Diagnostic criteria of UTI	Symptoms and signs
North 1963 [60]	ED or O/P USA	82 febrile children (>38^{o}C) aged under 13 years. 3 UTI.	Catheter or clean catch	Symptoms and signs not clearly presented. States 'only 1 had signs and symptoms of acute pyelonephritis. The others did not develop clinical evidence of infection'
Krober 1985 [61]	Hawaii Army centre	182 infants <3 months old with fever >=38.0^{o}C. UTI in 20.	Catheter urine >10^{4}cfu/m	No symptoms or signs given. Only that non-circumcised males were more likely to have UTI.
Grundy-Wheeler 1987 [62]	GP UK	104 children. 17 with UTI. Aged under 12 years	Culture MSU. >10^{5}cfu/ml	'All those with UTI either had an illness clinically suggestive of this diagnosis or had some degree of abdominal pain or tenderness as a feature of their illness'.
Crain 1990 [63]	Pediatric ED USA	442 febrile infants (>38.1^{o}C) Aged less than 8 weeks. 33 with UTI	Dipslide culture. Catheter >=10^{4}cfu/ml; SPA >=10^{2}cfu/ml; bag specimen >=10^{4}cfu/ml	Found that impression of sepsis, WBC count and ESR were not useful for identifying UTIs'.
Fallahzadeh 2006 [64]	Iran Hospital	120 Aged between 4 weeks and 5 years with diarrhoea. 120 controls healthy children from nurseries. 8 patients with UTI	MSU or bag. 2 positive cultures with >10^{5}cfu/ml with similar sensitivity patterns	88% fever, 63% vomiting
Baker 1993	ED USA	Rectal temp >38.2^{o}C 747 infants age 1-2 months old	Catheter sample >1000 cfu/ml of a single organism.	No symptoms or signs given.
Bonadio 1993 [65]	ED USA	233 febrile infants aged 0-8 weeks. Fever >38.0^{o}C	Urine culture from catheter specimen >=10^{5} cfu/ml single species.	No symptoms or signs given. Reports the use of a scale for assessing serious bacterial illness.

Lead author and date	Setting	Age and sample size	Diagnostic criteria of UTI	Symptoms and signs
Bonadio 1993 [66]	ED USA	447 febrile infants aged 0-8 weeks. 36 with confirmed UTI	>= 10^4 cfu/ml from catheter spec or >=10^3 from SPA	No symptoms or signs given.
Hoberman (see above table)				
Bonadio 1994 [67]	ED USA	356 febrile infants aged 8-12 weeks. 17 with confirmed UTI. Rectal temp >38.0°C	>= 10^4 cfu/ml from catheter spec	No symptoms or signs given.
Shaw 1998 [68]	ED USA	2411 febrile children (≥38.5°C); Boys <1 year and girls <2 years old.	Catheter	UTI more common in girls, white race, no potential source of fever, Ill appearance, not circumcised, fever >39, PH of UTI, abdominal tenderness, and presence of urinary symptoms. They do not present % or RR of symptoms, only prevalence of UTI in the various sub-groups.
Gorelick 2000 [69]	Pediatric ED USA	1469 girls younger than 2 years with fever (>=38.3°C) and no unequivocal source of fever. 63 with UTI	>10^4cfu/ml catheter urine	Found that UTI was associated with age less that 12 months old, white race, temp of 39.0°C or higher, fever for 2 days or more and absence of another source of infection on examination.
Herr 2001 [70]	ED USA	434 infants <60 days with fever (>=38.0°C). 25 with UTI	>50 000 cfu/ml catheter specimen	No symptoms or signs given.
Maniaci 2008 [71]	ED USA	234 febrile (>=38.0°C) infants <90 days. Excluded infants with focal bacterial infection (other than otitis media). 24 with UTI	Catheter urine >= 50,000 cfu/ml or 10,000-49,000 with positive urinalysis.	No symptoms or signs given. The focus of the study was procalcitonin levels.

Shaw et al found that infants without a potential source of fever were more likely to have a UTI (5.9% of 474 with no potential source of fever had UTI vs. 2.7% of 1858 with a potential source of fever; p<0.001). However, given the large number of presenting infants with a potential alternative source of fever, this feature is less helpful when trying to rule out UTI, and ensuring that no UTI is missed. Using the numbers provided by the authors, this equates to only 36% of children with UTI presenting without an alternative potential source of fever.

Shaikh et al published a systematic review of the diagnostic accuracy of symptoms and signs for the diagnosis of UTI in infants and children.[72] The authors reviewed 12 articles which met their inclusion criteria. Eight of the studies included children only aged under 24 months old. Nine studies only included children if they had a fever of >=38.0^{o}C. The prevalence of UTI found in studies ranged from 3.3 – 13.8% suggesting variation in sampling or population. Seven of the studies were conducted in ED departments. The others were in 'office' setting which may indicate primary care or secondary care outpatient clinics. Eight studies describe urine collected with catheters or SPA. All but two studies were considered by the authors to have sampled urine from consecutive children. However, they were interested in 'consecutive patients suspected of having a UTI', therefore studies could be included if children had urine sampled based only on level of clinical suspicion for UTI or specific urinary symptoms.

For example, one of the papers (Dickinson (1979) conducted in general practice in the UK, included children aged under 15 if the *GP suspected them* of having a UTI, but in the quality rating was considered to have included consecutive children.[51] However, eight of the 12 included studies did appear to have systematic urine sampling from febrile children which was independent of clinician suspicion of UTI.[48 61 67 68 73-76] In addition to Dickinson's study, Newman, Heale and Chen's studies reported results where urine samples were obtained based on clinician suspicion of UTI.[51 77-79] Struthers describes children in a paediatric acute admissions unit, so children had already been selected for admission by GPs or ED staff, but once admitted they did have urine sampled systematically.[75]

The systematic review reported by Shaikh et al found that in febrile infants up to 2 years old, a history of previous UTI, non-black race (which was not fully explained by circumcision status), a temperature of higher than 40^{o}C, prolonged fever for >24 hours, suprapubic tenderness and lack of circumcision increased the probability of UTI.[72] They found that "the presence of another source for fever (e.g. otitis media, URTI, gastroenteritis) reduced the

probability of UTI only to a small extent". They found that in verbal children (>2 years old) that abdominal pain, back pain, dysuria, frequency, and new onset urinary incontinence increased the probability of UTI.

The authors comment that 'because the negative Likelihood Ratios (LRs) for all studied symptoms were more than 0.60 and often approached 1.00, the absence of individual symptoms does not substantially reduce the likelihood of a UTI'. However, they conclude that 'the absence of several key signs and symptoms in combination can be used to identify infants at low risk for UTI'.[72]

The issue of fever

Most of the studies described only include febrile children. There are several problems with this. The first is the definition of fever. Some authors define what they mean by fever and some do not. The definition of fever can vary widely[80], temperature fluctuates during an illness and can be affected by medications. In most of these studies discussed here it is defined as >38.0^{o} C. The NICE guideline (UTI) table considers any description of fever together, both temperatures >38.5 and <38.5^{o}C.[1] Temperature can also vary widely depending on the instrument used and where the temperature is taken from. Manufacturers of commonly used infra red ear thermometers give wide 'normal' ranges of temperatures making interpretation difficult. Many studies do not describe methods in detail. Therefore populations of 'febrile children' may be quite heterogeneous.

Secondly, there is evidence that renal scarring and complications from UTI can occur in the absence of fever.[81] The systematic review by Shaikh et al found that neither the rate of pyelonephritic abnormalities nor the rate of renal scarring on DMSA were associated with presence or absence of fever.[11] However, as the majority of studies concerning UTI and renal scarring exclude children without fever, the association of fever with renal scarring and complications will continue to be unclear.[81]

Presence or absence of an alternative source of infection

Current, and previous guidelines, state that UTI is unlikely if there is evidence of a potential alternative source of infection, and do not require urine sampling (at least initially) in these children.[1] This belief is also held by practice nurses who are often involved in triage.[82]

However, there is evidence that UTI occurs in children *with* other sources of infection. In addition, the presentation of findings in studies can lead to different interpretations and different emphasis.

Shaw, Hoberman and NICE conclude that UTI is more likely if there is no potential alternative source of infection.[1 48 68] However, if you look at the numbers, Shaw found only 36% of those with UTIs had no alternative potential source of infection.[68] The vast majority of UTIs would be missed if a strategy of not suspecting/not sampling urine from children with an alternative potential source of infection.

Hoberman found that UTI was twice as common in febrile infants with no identified source of fever as those with an identified source (7.5% vs. 3.5%; p=0.02).[48] Put another way, 34/50 (68%) with UTI had no potential alternative source of infection. Thirty-two percent of UTIs would have been missed if urine was not sampled in those with a potential alternative source of infection.

Of course, it depends what is included as a 'possible source of fever', who is assessing this and inclusion criteria of the study (Shaw and other studies exclude those with an 'unequivocal source of fever'). Hoberman describes unequivocal sources of fever to include meningitis, pneumonia, septic arthritis, varicella and possible sources of fever to include URTI, gastroenteritis, otitis media, croup, bronchiolitis, and viral syndrome.[48]

Torrijos et al found that 16% of children with otitis media also had UTIs.[83] Other studies have found that the prevalence of UTI in children with URTI is as high as 30% .[84] Bauchner et al found that all their cases of UTI in infants had originally been diagnosed with alternative infections (n=11/11 out of 664).[85]

Gorelick et al found that risk of UTI was greater if there was no other potential source of infection (RR 1.9; p=0.01).[69] The number of children overall with UTI was 63 (4.3%). Overall, 77% had a potential source of fever on examination, with only 23% having no alternative source of fever. Unfortunately they did not give the numbers of children with UTI with and without an alternative source of infection, so I cannot work out the proportion of those with UTI without an alternative source of infection. However, given the low percentage of presenting children without a potential source of infection, I suspect they will not have

found it to be effective at ruling out UTI either. Shaikh et al's systematic review concludes that, "the presence of another source for fever (e.g. otitis media, URTI, gastroenteritis) reduced the probability of UTI only to a small extent".[72]

Unfortunately, the findings that UTI is more likely in a child with no alternative source of infection, even if the majority of children with UTI may have an alternative site of infection, has led to current guidelines suggesting that children with an alternative source of infection do not need to have their urine sampled (at least on initial consultation).[1]

Urine sampling

For current diagnosis of UTI, a urine sample needs to be obtained and sent to the laboratory for culture.

There are five main methods of obtaining urine samples from children: suprapubic aspiration, catheter insertion, clean catch, nappy pad, and bag collection. Suprapubic aspiration (SPA) is considered to be the gold standard method, as it is aseptic and (supposedly) avoids the issue of contamination. However, it is an invasive test, requires training and is only feasible for hospital environments. Using a catheter is also invasive and distressing for children and not feasible for use in primary care. The three remaining methods are non-invasive and have been used in primary care. However the clean catch method can be time-consuming for parents, and the urine collection bags have been found to be unpleasant for the child. All three methods have a risk of contamination, but the clean catch method has been found to be associated with the lowest levels of contamination.[1] The NICE guidelines published in 2007 recommend clean catch to be first choice, and a nappy pad as second choice if clean catch is not possible or acceptable.[1]

Once the urine sample is obtained, it needs to be placed in a suitable container to be sent to the laboratory. Urine samples collected in primary care can rarely be cultured immediately. There is a delay between the sample being collected from the child and collection from the surgery and transported to the laboratory. There is further delay once the sample is received by the laboratory but before it is cultured. Bacteria present in the urine sample at the time of voiding, do not stay in the same state, but multiply. The growth is exponential and numbers depend on the time between when the sample was voided and the time at which the culture

and count is measured. The growth rate of the bacteria also depends on the temperature and can be affected by the presence of other substances (e.g. boric acid).

Contamination

If a urine specimen comes into contact with bacteria from the skin or bowel, these bacteria can be taken up into the urine, grow during the culture process, and may be found in significant numbers. These growths do not represent a UTI but are just due to the 'contamination' of the urine sample. It can be difficult to differentiate between growths of contaminating bacteria and growths of bacteria representing a true UTI.

If there is a mixed growth, with several different species of bacteria present, this is considered more likely to be a contaminated sample. Sometimes the type of bacteria found is used to determine whether it is likely to be a contaminant. For example, bacteria known to be skin commensals which are not usually thought to cause UTIs, are likely to be considered as contaminants. Sometimes there are large numbers of epithelial cells present in the sample which indicates that the urine is likely to be contaminated with skin bacteria. The difficulty with these approaches is that just because there is contamination of the specimen with other bacteria, does not exclude a true UTI as well but which is hidden or disregarded due to the contaminants; some bacteria can act both as non-pathogens and pathogens in some case (e.g. coagulase negative staphylococcus aureus); bacteria found in the bowel which are likely to contaminate urine samples, especially those from nappy pad samples, are those which are often the cause of UTI. This is particularly difficult in the presence of diarrhoea, which will increase the likelihood of contamination but is also a potential risk factor for developing UTI.

Giddens (1998) describes a contamination rate of 66% in children under 2 years old.[86]
But the problem is largely one of definition of contamination, and this varies between laboratories and researchers.

Diagnosis of UTI

UTI is usually defined as a pure or predominant growth of bacteria of more than 100,000 organisms per millilitre (>10^5 org/ml) on urinary culture.[1] However, different cut off points have been used and proposed.[16 87 88] What constitutes 'pure or predominant growth' is not clearly defined. Whether this is simply the most common organism found, the growth of any

organism over a certain threshold or whether it is the most common organism when there are only two organisms present and the other is in very low quantities, is not clear. The NICE guideline does not define predominant growth.[1] Neither does the UK Standards for Microbiology Investigation of Urine, although this document includes in the appendix a complex table for interpretation of urine culture. [89] The local laboratory SOPs do not define what is meant by pure, predominant or mixed growths.

The Quandary

It is difficult to know if finding bacteria in the urine represents a true UTI. It is also difficult to be sure that absence of bacteria in the urine means there is not a UTI. Contamination of the urine sample with other bacteria from skin, vagina or rectum can cause false positive or false negative results.[90] A true UTI may be present but there may be only low counts of bacteria found on culture for various reasons (discussed later). True bacteriuria can be found in the absence of any evidence of inflammation in the patient, this is known as 'asymptomatic bacteriuria' and the significance of this is disputed.

As with other infections, there are cases where there is a definite infection, cases where there is clearly no infection, and a range of cases where it is less clear whether infection is present or not. There may be clinical (visible) features of the infection and there are the results of tests used to diagnose or quantify the infection in a more objective manner. The clinical features are subjective, both to the patient and the clinician; the diagnostic tests are not 100% accurate, depending both on the inherent validity of the test and the way in which it is used and read by the clinician. All of this introduces uncertainty into the accuracy of the diagnosis for infections in general. However, in the case of UTI in children, the uncertainty is even greater due to a number of factors, many of which have already been discussed:

- The clinical symptoms are often not apparent. Infections of other parts of the body are usually obvious, for example skin infections or tonsillitis, where the tissue is red and hot and there is pus present, or infection in the intestines where there is diarrhoea and vomiting. UTI in adults also causes typical symptoms, namely urinary frequency, dysuria and abdominal pain (often localised to the suprapubic or loin regions). Unfortunately UTI in children does not usually cause these localised symptoms.[1] The symptoms and signs associated with UTI in children are non-specific, similar to those

found in many other common childhood illnesses. The most commonly documented are fever, irritability, malaise and lethargy.[1]

  - Fever, often an important or essential component to the diagnosis in the literature, is defined variably and sometimes not at all.[1 80]
  - The method for measuring temperature is also often not clearly described or specified, and different instruments and measurement in different areas of the body result in large differences in the temperature found.[80]

- The GP or nurse needs to consider the possibility of UTI and request a urine sample.
- Obtaining a urine sample from the child can be difficult, particularly in primary care, where there is often no spare room (other than the toilet) for the child and parent to go to obtain the urine, and practices may not have the necessary paediatric equipment (large sterile bowl for clean catch or nappy pads for non-toilet trained babies). Time may also be a problem.
- Once the urine sample has been obtained, the urine has to be sent to the laboratory for the diagnostic test (culture). The sample may be affected during this process depending on the type of storage (e.g. whether boric acid has been added), how the sample is stored whilst waiting for transport (e.g. kept in freezer or by warm radiator in the surgery), how long it takes to be collected and transported to the laboratory and how long it is between reaching the laboratory and being tested.
- The test itself (urine culture) is designed to detect the presence of bacteria in the urine sample. It involves spreading a known volume of urine onto a culture medium and leaving this in an incubator for 18-24 hours. The number of bacterial colonies are then counted (by eye).
  - The number of bacteria secreted from the urinary tract into the urine will depend on the type of bacteria (e.g. some with fimbriae may be more firmly attached to the bladder wall and be secreted less), factors specific to the individual infected (some people may be better than others at clearing the bacteria from the urinary tract, variation in inflammatory response and cell shedding), the concentration of the urine (fluid intake), presence of other substances ingested (antibiotics, cranberry juice, others), and the stage of infection (perhaps fewer bacteria are secreted in the early stages and more when bacterial load is greater).

- The number of bacteria in the urine at the time of testing is dependent on the number of bacteria secreted from the urinary tract into the urine, contamination of the urine sample with bacteria from places other than the urinary tract (skin, nappy, GI tract etc), the growth rate of the bacteria in the urine, the time taken to reach the lab, the conditions it is kept in during transport (temperature, boric acid), and time taken from reaching the lab to starting the processing.
- The detection of bacteria in urine is dependent on the numbers of bacteria in the urine at the time of testing, the culture medium used, the type of bacteria (some may not grow at all outside of the body; some may grow better outside of the body than in the bladder), growth rate of the bacteria in that medium, the temperature during the culture period, and the time at which it is read.

Therefore even ignoring those cases in which the possibility of UTI was not raised and a urine sample was not requested, or those cases where a urine sample was requested but not obtained, there is still a significant degree of uncertainty surrounding any urine culture result.

Causative organisms

Most UTI are caused by uropathogenic *Escherichia coli (E.coli*; UPEC).[91] A retrospective UK study of 547 UTI cases (337 children aged <16 years) conducted in 2002-2008 found that 92% of UTIs were caused by *E.coli*.[92] A prospective study in Brussels of 209 children (aged <17 years) with their first febrile UTI conducted in 2006-2008 found that the causative organism was *E. coli* in 91%.[93] A retrospective study of 533 children (aged 6 months-6 years) conducted in 2001-2006 in the USA, found that the causative organism was *E. coli* in 80%.[94] A Canadian study of 173 children (<18 years old) in 2004-2005 found a pure growth of *E. coli* in 74% of UTIs.[95] A study of 141 hospitalised infants less than 2 months old found that the most commonly identified bacterium was *coagulase-negative staphylococcus* (found in 28%).[96] The problem with these studies (except for the study of infants <2 months old) is that the urine sampling was not systematic. In addition, most included children were aged up to 16 or more.

Furthermore, the laboratory culture methods have been established to detect *E.coli* UTIs with counts of more than 10^5 bacteria/ml.[97] Even if a greater proportion of UTIs is caused by

organisms other than *E. coli*, they may not be detected, and could be reported as culture negative UTI or not classified as UTI at all.

There seems to be a trend towards a greater proportion of non-*E.coli* UTIs in younger children.[94 96] Friedman et al found that children with non-*E.coli* UTIs were younger.[98] They also found that non-*E.coli* UTI was more likely to be associated with VUR, as have other studies.[99] Honkinen et al (1999) found that VUR was nearly twice as common in children with non-*E.coli* UTIs.[99]

Kanellopoulos et al (2005) found that low count UTIs are often due to non-*E.coli* bacteria.[16] They showed that these types of UTI were more likely to affect infants and young children and were associated with the same clinical findings and outcomes as higher count UTIs.

Many studies reporting UTI define UTI as $>10^5$cfu/ml *of a uropathogen*.[68 100-103] However, there are no agreed lists of which organisms are uropathogens and which are not. The Cardiff and Vale Laboratory Standard Operating Procedure (SOP) includes a list of 'potential isolates' which includes *Enterococci, Lancefield Streptococcus group B, Coagulase* negative *staphylococci, Staphylococcus aureus, staphylococcus saprophyticus, Enterocbacteriaceae* (including *E.coli), Pseudomonads* and Yeasts (Appendix 1.1).[104]

As mentioned before, organisms can sometimes be uropathogenic and sometimes not. *Coagulase negative staphylococcus* is often not considered a pathogen but sometimes is considered to be an important uropathogen.[90 96] Table 1.4 shows the proportion of *E.coli* and non-*E.coli* UTIs.

Table 1.4: Proportion of UTI caused by various bacteria in different studies

Lead author and date	Number of UTI cases and age range	Proportion of UTI caused by *E.coli*	Proportion of UTI caused by other gram negative pathogens *	Proportion of UTI caused by gram positive pathogens **	Proportion of UTI caused by other/unknown pathogens
Honkinen 1999 [99]	1237 children (age not given)	79%	13%	4%	4%
Friedman 2006 [98]	139 <16 yrs	77%	23%		
Chakupurakal 2010 [92]	547 <16 yrs	92%	5%	1%	2%
Nowell 2010 [96]	141 <2 months	Most common bacteria (28%) *coagulase negative staphylococcus*			
Paschke 2010 [94]	533 6 months-6 yrs	80%	15%	Gram positive or unknown 5%	
Weisz 2010 [95]	173 <18 yrs	74%	13%	6%	
Ismaili 2011 [93]	209 <17 yrs	91.0%	8.5%	0.5%	0%

* includes most commonly *Pseudomonas, Klebsiella, Proteus, Enterobacter, Citrobacter, Haemophilus*

** includes most commonly *Streptococcus, Staphylococcus*

Definition and threshold

Kass established the threshold value of 10^5 bacteria/ml more than 50 years ago.[105] This level was based on studies of adult women with acute pyelonephritis and asymptomatic women found to have bacteriuria on repeated urine samples. He found that 95% of those with acute pyelonephritis had bacteriuria with more than 10^5 bacteria/ml, and that using this threshold seemed reliably to distinguish between bacteriuria and contamination.[97 105 106]

Stamm (1984) points out that this threshold may not be appropriate for patient population different from the ones Kass studied.[107]

Studies of adult women with lower UTI (i.e. not pyelonephritis and not asymptomatic bacteriuria) have found that up to 50% have counts of less than10^5 bacteria/ml on culture.[106] Stamm et al examined the urine of 187 women with acute urinary symptoms obtained by

SPA or catheterisation and compared this to mid-stream urine specimens obtained at the same time. Forty-nine percent of women with coliforms in the bladder urine specimens had less than10^5 coliforms/ml on MSU.[106] They found that the 'the traditional criterion of >10^5 per millilitre provided a specificity of 0.99 but a sensitivity of only 0.51. They propose a threshold of more than 10^2 per ml with a sensitivity of 0.95 and a specificity of 0.85 (for coliform UTI in adult women).

Kass acknowledged that using his threshold of more than10^5 bacteria/ml would miss some women with an infection. He also suggested that recent use of antibiotics, drinking lots of water and urine with low pH or high urea concentration would make a low count more likely despite an infection being present. [108]

Stamm et al also found that presence of more than one organism should not necessarily be regarded as a contaminated sample and could represent a true UTI.[106] Lau et al (2007) comment that samples with mixed growth are generally assumed to be contaminated but, "infants with low count UTI may yield mixed growth when the true causative organism was masked by contaminating flora". They also point out "that genuine mixed infections may have occurred".[90]

Many of these studies included only adult women and may not necessarily be generalisable to children. In fact, it may be that the cut-off developed by Kass for adult women should not have been established as the standard for the diagnosis of UTI in children and may need to be revisited. Given that infection can be present at lower counts and in the presence of more than one organism in adult women, perhaps the same is true of children.

Pryles (1960) describes a small study of children (n=17) where 3(18%) children had clinical evidence of UTI but colony counts between 10^3 and 10^5 cfu/ml. These patients were all found to have colony counts of more than10^5 cfu/ml on subsequent urine specimens.[109] Pryles suggests that urines containing bacterial growths of less than10^3 cfu/ml imply contamination; counts of more than10^5 cfu/ml imply infection and counts in between are "to be suspected of infection and repeated". [109] Hellerstein (1982) used a threshold of 10^4 cfu/ml in catheter specimens.[110] Hoberman et al (1994) describe a study of 2184 (catheter) urine samples from children less than 24 months old.[111] They found that bacterial counts of less than10^5 cfu/ml of a single pathogen were uncommon and that specimens with counts between 10^3 and $5x10^4$

were more likely to be caused by gram-positive or mixed organisms. They suggest using a threshold of $5x10^4$ cfu/ml.[111]

Hansson et al (1998) found that 20% of infants had less than10^5cfu/ml of bacteria on culture of urine obtained by SPA.[88] Kanellopoulos et al (2005) showed that UTI could be present despite low urinary bacterial counts (from catheter or SPA specimens), and found that low count infections were more common in infants and young children (<24 months old) and were often caused by non-*E.coli* species. There was the same risk of scarring and other findings in the low count group as in higher count infections.[16]

Lau et al (2007) compared bacterial cultures obtained from clean void urine samples with catheter samples (n=98).[90] They found that there was no difference between catheter urine specimens and clean voided specimens in terms of false positive results for lower threshold values of 10^3 or 10^4 cfu/ml if mixed growth results were considered contaminants.

NICE points out that low counts of bacteria (<10^5cfu/ml) and mixed growth results can indicate a UTI, but that the chance of bacteria representing contamination increases as the threshold value is lowered. They comment that, "the results from urine culture can therefore not be interpreted in isolation, but should be done in relation to the clinical setting, symptoms and findings."[1] However, there have been more recent suggestions that a lower threshold should be used in children even when urine samples are obtained with non-invasive methods. It has also been suggested that a higher cut-off point should be used in order to reduce false positive results.[87] Coulthard et al advocated increasing the cut-off value for diagnosing UTI from a single urine sample to more than10^6 cfu/ml.[87]

Multiple urine samples

Some studies have required two consecutive urine samples that culture more than 10^5 cfu/ml of the same bacteria to define a UTI.[56 87] These are secondary care studies. Kass required two samples to grow the same bacteria for a diagnosis of (asymptomatic) bacteriuria in adult women. Some advocate that two samples should be required in primary care paediatric samples as this should reduce the risk of false positive results.[87] The NICE guidelines require one sample with more than10^5 cfu/ml.[1]

Coulthard el al (2008) used two consecutive urine samples to determine 'true' UTI.[87] They argued that if the first sample is positive, but the second sample is negative or grows a different bacteria, that the first sample was contaminated and indicated a false positive result. This is one explanation for finding that the two samples were different. However, it could also be that for some of the reasons already mentioned, one of the results was falsely negative.

The problem of whether two samples are needed for diagnosis is related to the problem of where the cut-off value should be for bacterial count. The problem is that in reducing the chance of false positive results (improving the specificity), we are likely to increase the chance of false negative results (reduced sensitivity). It is a balance and trade-off. The risk to patients is of unnecessary antibiotics and investigations if they are given a falsely positive result, and an untreated UTI, longer duration of illness and possibly long term complications if they are given a falsely negative result. The cost to the NHS is of unnecessary antibiotics and threat of antimicrobial resistance and costly investigations for false positive results and of possible repeat consultations or hospital admission for an untreated infection and the potential risk of extremely high costs related to long term and chronic complications in some children with a false negative result.

Near patient tests

Dipsticks in primary care

A systematic review by Whiting and other studies led NICE to conclude that urinary dipstick tests should not be used in children under two years old as they are unreliable.[1 112] For children older than two years, a positive leukocyte esterase and nitrite can reliably be used to diagnose a UTI, and if both of these tests are negative, a UTI can be ruled out with adequate confidence.[1]

Microscopy as a near patient test

Following a comprehensive review of studies, NICE concluded that it was difficult to be clear about the diagnostic accuracy of microscopy. However, they found that microscopy was better than dipsticks.[1]

Self-limiting UTI

It is difficult to know if UTIs in children are self-limiting, as any identified UTI is usually treated promptly with antibiotics. There are no randomised controlled trials of antibiotics compared with placebo in the treatment of UTI in children or observational studies of the outcomes of those with confirmed UTI not treated with antibiotics. Therefore, I could not find any direct evidence that UTIs in children are self-limiting. However, it is likely that some UTIs in children are self-limiting. There is evidence that UTIs in adults are often self-limiting.[113 114] In addition, if there are many UTIs being missed, as suspected, it seems likely that some of these children must have resolved spontaneously, or else they would have re-presented. Some patients recover from all types of bacterial infection and childhood UTI is probably no exception. Some children with UTI would probably have been given antibiotic treatment if they were suspected of having different diagnoses by their doctor but it seems unlikely that this would have happened with all childhood UTI not detected.

One prospective study of feverish illness in children under five presenting to the ED found that "one third of children with serious bacterial infection appeared to recover spontaneously without antibiotics".[47] Some of these may have had UTI.

The important question is, if a child has a self-limiting UTI, and they recover clinically, are they still at risk of renal scarring and long-term complications?

In half of adult women, bacteriuria persists following a symptomatic UTI if this is left untreated, even if their clinical symptoms have improved.[91] An experimental study of pigs found that renal scarring could occur even when clinical, symptomatic recovery had occurred.[115]

To be able to describe the natural history of untreated UTI in children would require identification and confirmation of UTI with culture and then observation of symptoms and signs without antibiotic treatment and long term follow up to identify any scarring and complications. To confirm the benefit of antibiotic treatment both in the acute illness and in the prevention of complications would require a randomised placebo controlled trial. Studies which involved non-treatment or placebo treatment in children with confirmed UTI would not be ethical to do given the current widespread belief that UTI may lead to long term

complications and some indirect evidence that antibiotics are likely to help the acute illness, relieve suffering associated with this and possibly reduce the risk of serious complications.

Asymptomatic bacteriuria (ASB)

Definition

Asymptomatic bacteriuria (ASB) is the growth of bacteria of more than10^5 orgs/ml on culture of urine in a patient with no symptoms. Guidelines recommend that ASB is not treated with antibiotics in infants and children.[1] The population of children that are the focus of my thesis are all acutely unwell, and therefore are not, by definition, asymptomatic. However, ASB may still be relevant because an acutely unwell child could have an underlying ASB with a coincidental acute illness unrelated to the bacteriuria.

Although the definition of ASB appears to be clear, in practice there are various possible explanations for a finding of significant bacteriuria in an asymptomatic patient:

- It could represent true ASB, that is, bacteria present in the urine in numbers usually associated with symptomatic UTI but without symptoms.
    - It could be due to the presence of bacteria but which are harmless to that person, perhaps part of the normal flora.
    - It could be due to a problem with the person's immune response, perhaps for some reason they do not mount an inflammatory response to the invading bacteria and so there are no clinical signs of an infection.
    - It could also be the early stages of a UTI – there are enough bacteria to be found on culture but not quite enough time for an immune response to have been mounted and cause symptoms.
    - There may be an immune response occurring but the symptoms have gone unnoticed or unreported.
    - It could represent the end of a UTI. Perhaps the clinical symptoms have cleared but there is still evidence of bacteria.

- The bacterial count may not represent the true levels of bacteria in the urinary tract
    - Bacteria from elsewhere could have contaminated the sample, grown in the urine during transport and storage and then grown on culture.

The diagnosis of ASB is even more difficult in an acutely ill child. In addition to the difficulties of diagnosing ASB in an asymptomatic child, it is impossible to distinguish between a child who has a symptomatic UTI and a child who has an ASB with a coincidental other illness, because the presenting symptoms of UTI are non-specific.

Prevalence of ASB

Several studies, most from the 1970s, have reported the prevalence of ASB. Some of these are summarised in Table 1.5, although this is not a comprehensive review of ASB prevalence.

Table 1.5: Prevalence of ASB in children

Author & year of publication	Age of children	Number screened	Prevalence of ASB	
			Female	Male
Savage 1973 [116]	5 years	5217	1.6%	-
Davies 1974 [117]	1 month-5 years	507 528	0.8%	0.2%
McLachlan 1975 [118]	4-12 years	16800	1.7%	-
NABR* 1975 [119]	4-6 years	2398	1.4%	-
	7-11 years	5372	2.5%	-
	12-18 years	5694	1.6%	-
	5-18 years	1595	-	0.2%
Saxena 1975 [120]	Pre-school	1000	0.5%	
Silverberg 1976 [121]	2-5 years	2197	1.3%	-
Siegel 1980 [122]	0-1 years	1617	1.8%	0.5%
	Pre-school	1711	0.8%	0%
Goosens 1985 [123]	3-36 months	441	0.4%	2.5%
Wettergren 1985 [124]	0-2 months	3198	0.2%	1.6%
	2-8 months	3089	0.2%	0.8%
	8-15 months	2546	0.5%	0.2%

* Newcastle Asymptomatic Bacteriuria Research Group

Studies varied in the techniques used to sample urines (SPA, catheter and bag urines) and in the number of consecutive samples showing significant bacteriuria required for a diagnosis of ASB.

Those with ASB are a heterogeneous group as described above. NICE point out that children found to have ASB during screening will include "those with no discernable history of UTI, some with a previous history of UTI, and some who have had symptomatic UTIs but have not been diagnosed".[1] The authors of a Cochrane review of interventions for covert bacteriuria in children comment, "In some previous studies, children identified with bacteriuria and no apparent accompanying symptoms later described mild urinary symptoms at the time of testing".[125]

Current opinion[126] and current guidelines[1] suggest that antimicrobial treatment and follow-up is not indicated for asymptomatic children found to have significant covert bacteriuria. Comprehensive reviews of the prevalence and risk of long-term complications for ASB are not presented in the NICE guideline document, and only one of the four studies concerning ASB prevalence discussed in the NICE guideline includes children less than four years old.[124] NICE reviewed four studies of antibiotic prophylaxis for children with asymptomatic bacteriuria, and found that antibiotic prophylaxis reduced bacteriuria but did not reduce recurrence of symptomatic UTI.[127-130] However, none of these studies included children aged less than four years old.

A recent Cochrane review concludes that, "studies do not provide sufficient detail about the harms and benefits of treating covert bacteriuria to enable forming reliable conclusions."[125] However, they also point out that there is no evidence of harm in schoolgirls with ASB not treated with antibiotics. The studies included in this review were girls aged 5-12 years with 4 year follow-up, n=208;[131] girls aged 4-18 years with 5 year follow-up, n=199;[129] and girls 5 years with 2 year follow-up, n=42.[130] These results may not be generalisable to children (boys and girls) less than 5 years old.

I could not find any recent reviews of treatment of ASB which included studies of children less than 4 years old. A review in 1990 concluded that neonates and preschool children with ASB *should* be treated.[132] I found one study which followed up infants with ASB for 6 years. None of the 9 girls and 27 boys had renal damage on follow up urography, although some

developed pyelonephritis.[133] Numbers were small and some of the infants had received antibiotics for RTI.

For children less than five years old, the prevalence of ASB is likely to be less than 1.5% (see Table 1.5). It is unclear whether ASB in infants and young children is beneficial or not. Screening is no longer recommended or practiced, and the issue of whether to treat ASB or not is only relevant in a clinical context where children are generally unwell and where the distinction between ASB and UTI is difficult.

For an acutely ill child presenting to their GP, who is found to have significant bacteriuria, the possibilities are:

1) a true UTI
2) a different illness + a contaminated urine sample causing significant bacteriuria
3) a different illness + coincidental ASB

In practice, and according to current guidelines, an acutely ill child with a growth of $>10^5$ cfu/ml bacteria in their urine would be considered to have a UTI and would be treated with antibiotics.

Laboratory tests

Current recommendations

The definition of UTI is the growth of $>10^5$ colony forming units (cfu)/ml of urine following culture. The process of how the urine is cultured, what medium it is grown on, the temperature it is incubated at and the time for which it is left to grow will affect the number of bacterial colonies found. It is therefore essential that standard methods for culture and reporting are used. Laboratories have standard operating procedures (SOPs) detailing exactly how these processes should be carried out. There are different methods used for different types of urine specimens (suprapubic catheter specimens, bag specimens, urostomy urines etc). There are sometimes different procedures depending on the clinical information given. Different laboratories have different SOPs, and some vary in their methods.

In the Cardiff and Vale SOP (Appendix 1.1)[104]. Method 1 (in this document) would be used for MSU or pad urine. This consists of using a ‘dip strip’ which is dipped into urine up to a

mark. This is then pressed flat against the agar for a 'few seconds'. Ten samples are inoculated on to one CLED plate. For neonatal urine samples and SPA samples, a different method is used as lower bacterial counts are expected. A 10 microlitre loop is used and spread in zigzags across a whole CLED plate. However, if any of these samples (MSU/pad/SPA or neonatal) had positive microscopy counts (i.e. 10 or more WBCs per high power field), a 1 microlitre loop is used and spread in zigzags across a whole agar plate.

A CLED (Cystine-Lactose-Electrolyte-Deficient) agar is the standard agar plate used. This has a selective growing medium. It 'supports the growth of urinary pathogens and contaminants but prevents undue swarming of proteus species due to its lack of electrolytes'.[134] No single medium is likely to be able to support the growth of (and therefore detection of) all significant organisms. Some organisms may not grow at all or at a sufficient rate to be picked up on certain culture mediums (e.g. *haemophilus influenza, pneumococcus, staphylococcus saprophyticus*[135]). Other factors can also reduce the number of colonies found on culture:[134]

- increased urine output due to high fluid intake (also high urine flow)
- Urine pH of <5
- Specific gravity of <1.003.

Blood agar is used to identify fastidious organisms (those needing specific conditions to grow, perhaps particular media, longer culture, anaerobic conditions) but is not routinely used for urinary culture.

Plates are then incubated at 35^{o}C for '18-24 hours'. An additional six hours is perhaps unlikely to make much difference to fast growing *E.coli*, but could foreseeably make a significant difference in the resulting culture count for infections with other organisms. Potentially significant isolates are listed as *Enterococci, Lancefield Streptococcus group B, Coagulase negative staphylococci, staphylococcus aureus, staphylococcus saprophyticus, Enterobacteriaceae (including E.coli), Pseudomonads* and yeasts.

Colonies are then counted. For the dipstick method, 1 colony is equivalent to 5,000 organisms/ml; 2 colonies equivalent to 10,000 up to 20 colonies equivalent to 100,000 organisms/ml and more than 20 colonies equivalent to more than 100,000 organisms/ml. For

the 1 microlitre loop method, 1 colony is equivalent to 1,000 orgs/ml; 10-100 colonies is 10,000-100,000 orgs/ml and >100 colonies are equivalent to >100,000 orgs/ml. For the 10 microlitre loop, 1 colony is equivalent to 10,000 orgs/ml.

Reporting varies depending on clinical information given on the form, for example if there is a growth of 100,000 orgs/ml but the WBC count <10, antimicrobial susceptibility testing may not be performed or reported unless the clinical information suggests UTI or the patient is compromised. Pure or predominant growth is not strictly defined. Mixed growths are reported as contaminants.

Could there be a better diagnostic method?

The standard diagnostic method (culture of urine) is far from perfect. If a suprapubic aspirate is used and examined immediately with methods which grow fastidious organisms (different growth media), and a low threshold for diagnosis, it is likely to be an accurate test for identifying bacteriuria with a low chance of false negative and false positive results. This could be considered the gold standard.

The reality, particularly in primary care with young children, is that the standard method falls short of a gold standard, with a high chance of false negative and false positive results. Even with the gold standard, there will be some cases where a true bacteriuria is identified but does not equate to a UTI, with no host reaction, no symptoms or inflammation.

With the standard method, there are likely to be contaminants which may hide a true positive result or lead to a false positive result. Urine sampling method, storage and transport will exacerbate the effect of any contaminants present in the urine sample.

Detecting host response or true infection rather than simply presence of bacteria is also flawed with the current method. Symptoms and signs are unreliable in children. Dipsticks for presence of white blood cells is unreliable in young children and so is microscopy for presence of white blood cells particularly if it is not done immediately.

Ideally a method is needed which detects bacteria accurately at the point of care. If bacteria are found in significant numbers in the urine immediately, it is less likely that contamination is the cause as they will have not had the chance to grow. PCR methods can detect any/all

bacteria present, but will also detect bacteria present in tiny numbers (e.g. contaminants). However, quantitative PCR methods may be possible. Currently these methods are not available at the point of care or cheaply, but this may be a possibility for the future.

Another possibility is to detect a host inflammatory response rather than detect the presence of bacteria. Microscopy or dipstick tests for white blood cells currently attempt to do this. This may also be achieved by detecting particular cytokines (chemicals released in an immune response) in the urine. This could potentially lead to a near patient test similar to a dipstick test. Again, there is nothing currently available but this may be a possibility in the future.

Another alternative is to improve the accuracy of the current test. Some possible options may include:

- Reducing the chance of contamination (perhaps by increasing use of SPA (unlikely in primary care) or improving cleaning prior to obtaining a specimen).
- Reducing the impact of contamination by reducing time from voiding to testing (perhaps by improved transport methods or within practice mini-labs).
- By stopping the growth of bacteria after voiding (by using preservatives like boric acid, refrigeration of samples in the practice and in the van until they reach the lab).

It is important to consider that the problems with the current method, particularly the impact of contamination, not only increases the likelihood of false positive results, but also of false negative results, as specimens containing mixed growths of bacteria are classified as negative. This is of particular concern in young children where false negative results could lead to a delay in treatment of a true UTI with possible long term complications.

Epidemiology of infections

What is an infection?

From the discussion above, it can be seen that it is not always clear when a UTI is present or not. In fact, the concept of an "infection", although commonly used and understood by healthcare workers and lay public alike, is not necessarily that clear. The difficulties with finding the causative organisms responsible for disease and distinguishing pathogenic from non-pathogenic bacteria has been a problem ever since micro-organisms were discovered.

The 'germ theory of disease' became established in the 19th century. Researchers in the 17th century were questioning whether an illness could be caused by micro-organisms. Antoni Van Leeuwenhoek (1632-1723) is considered to be the founder of microbiology.[136] He was the first person to observe and draw bacteria.[137] Further work by Andry (1658-1742), Bassi (1773-1856), Henle (1809-1885), Snow (1813-1894), Semmelweiss (1818-1865), Pasteur (1822-1895), Billroth (1829-1894), Klebs (1834-1913), Koch (1843-1910), and others led to the widespread acceptance that micro-organisms caused diseases.[137-139]

However, how can you determine if a particular illness ***is*** caused by a particular bug? Is it enough to find the presence of the bug at the same time as presence of illness? How unwell does the patient have to be and can there still be an infection if they are not unwell at all?

The difficulty of distinguishing between pathogens and organisms which were present but not harmful (commensal organisms) was a problem in the 19th century, and continues to be a problem in the 21st century.[140]

Koch developed a framework to help to determine whether a disease is caused by a particular micro-organism.

Koch's postulates

Koch's postulates (as stated in Fredrisks & Relman)[140] are:

1) The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease.
2) The parasite occurs in no other disease as a fortuitous and non-pathogenic parasite
3) After being fully isolated from the body and repeatedly grown in pure culture, the parasite can induce the disease anew.

A fourth postulate was added later:

4) The micro-organism must be re-isolated from the inoculated, diseased host.

Koch's postulates are still useful, but they have limitations which have become increasingly evident with the development of molecular microbiological techniques and understanding of the complex relationship between micro-organisms and human ('host-pathogen' interaction).[140] Some organisms cannot be grown in the laboratory or are difficult to grow

requiring special culture methods; an organism can be pathogenic in some circumstances and non-pathogenic in others; some organisms need another organism present to cause disease.[140] It can also be difficult to determine whether an organism is causing any harm or disease (subclinical infections or asymptomatic states). Whether an organism causes disease or not may depend on host factors including immune function, genetics and the organisms present in the normal flora.

Although molecular differences have been found between pathogenic and non-pathogenic organisms, the distinction is no longer clear, with organisms previously thought to be non-pathogenic causing diseases in some cases and pathogenic organisms not causing disease in some individuals despite being present in significant numbers on culture.[141] The issue of whether the presence of bacteria represents colonization or invasion is still a problem.[142]

Increased understanding of the complexities involved in the interaction between a human host and an organism, and the wide range of possible outcomes including sub-clinical immune response, full-blown inflammatory response and obvious clinical infection, non-symptomatic co-existence (asymptomatic carriage, commensalism, colonization or carrier state) and eradication of the organism, has made it increasingly difficult to be clear about definitions of previously widely understood terms like *infection* and *pathogen*.[141] The immune reaction to infection may be more (or as) important in the development of disease than the organism.[142]

These difficulties all apply to UTI and make definitions and diagnosis from a clinical or research point of view challenging.

Prevalence & incidence

The main aim of my thesis is to determine the *prevalence* of UTI among ill children presenting in primary care. Most of the studies which I have reviewed for my thesis consider the *incidence* or *cumulative incidence* of UTI. Whilst these terms are clearly related, there are differences which affect the calculation and interpretation of the data.

The incidence rate is the number of times a condition occurs in a given population and time frame. It is stated by Hennekens and Buring as "the number of new cases of a disease during a given time period divided by the total person-time of observation".[143]

For example, the number of new cases of UTI diagnosed among a population of 1000 children in a surgery over a year would represent the incidence rate. It is usually expressed as number of cases per 1000 person years which means the number of cases which would have occurred in 1000 people over a year.

Prevalence is the number of cases of the condition which are found when a cross-section of a particular population is considered. "Prevalence quantifies the proportion of individuals in a population who have the disease at a specific instant and provides an estimate of the probability (risk) that an individual will be ill at a point in time".[143] In this case the prevalence is the proportion of children found to have bacteriuria when they present with an acute illness to their GP. These cases of bacteriuria are presumed to be incident (new) cases of UTI by GPs and researchers, however they could be cases of longstanding asymptomatic bacteriuria coinciding with another acute illness.

As a GP, I want to know what the likelihood is of UTI in an acutely ill child presenting in my surgery. Of course, I really want to know how likely it is that UTI is the cause of the current illness. However, it is impossible, with current standard practice, to be sure that bacteriuria in the presence of an acute illness represents a UTI rather than a different illness with coincidental asymptomatic bacteriuria. But it is the *prevalence* of bacteriuria in presenting ill children which will give me the most useful information in determining what the chance of UTI is in a particular child. The prevalence of a condition is also known as the 'pre-test probability'.

Minimising bias in epidemiological studies

All research is subject to bias. Research concerning the determination of the prevalence of a condition and research concerning the risk factors or symptoms and signs associated with a disease are prone to particular types of bias. This has been a consideration when reviewing papers for the background section of my thesis, in the development of the study protocol and method, and during the analysis and interpretation of my data.

Grimes (2006) describes three main types of bias. [138]

1) Selection bias.
2) Information (observation) bias.
3) Confounding.

Selection bias

For many of the papers concerning incidence and prevalence, and in the design and interpretation of my research study, selection bias is one of the biggest concerns.

In most of the studies describing incidence, UTI is only detected in children who have had urine sampled following a decision by the clinician to obtain a urine sample because they already suspect a UTI. This could result in an erroneously high estimation because only those in whom the likelihood of UTI is high are selected to be the population in whom the incidence of UTI is calculated. Or it could result in an erroneously low estimation if the clinical suspicion is a poor indicator of UTI and so many children with UTI are unselected and their UTIs go undetected. Systematic sampling, obtaining urine from all children who present with all symptoms should avoid this particular type of selection bias. Unfortunately, even if a urine sample is requested on all children, it is not always possible to obtain one. If there is a reason for urine not being obtained which is associated with having (or not having) UTI, then there will still be selection bias. For example, if a child is more likely to be dehydrated if they have a UTI, and if it is more difficult to obtain a urine sample if a child has a UTI, then not obtaining a urine sample, because it is difficult, will result in UTI being missed as a result of selecting children in whom it is easy to obtain urine samples.

Selection bias could also result from including children (or not including them) with a certain feature, if this is related to UTI. For example if only febrile children are recruited into a prevalence study of UTI, if fever and UTI are associated, this would result in selection bias, if the population being studied is all children (with and without fever). On the other hand it is acceptable to only recruit febrile children if the study is about the prevalence of UTI in febrile children. However, the findings of such a study could not be generalised to non-febrile children.

Generally, a prospective cohort design will reduce the risk of selection bias because the exposures/risk factors are ascertained before the outcome of interest has developed. In the case of UTI, in a cross-sectional study, as the diagnosis of UTI takes time, the outcome is not known at the time of recruitment into the study.

Information (reporting) bias

Information bias can occur if there is systematic error in the way exposure or outcome is measured in the study groups. This can be caused by the instruments or diagnostic measurements or from the researcher or observer involved in the research. Bias occurs if errors affect one group more than the other.

Recall bias is a problem in retrospective studies, and less of a problem in the studies I have considered here.

Interviewer bias can occur if there is a systematic difference in the recording of or interpretation of data. This could be relevant in the studies I have considered, particularly during the assessment of outcome in prospective studies (for example if the person determining whether there is a UTI or not is aware of whether the child had had UTI in the past) or in the recording of exposures or symptoms in the case of retrospective studies if the person recording symptoms knew the UTI status. This type of bias can be reduced by blinding the researcher to outcome or exposure status.

In the studies concerning the long-term complications in which there is a long follow-up, loss to follow-up is an important issue and large potential source of bias.

An important consideration is mis-classification, which if systematic and associated with the outcome or risk factor, can cause bias. In the case of childhood UTI, given the problems with diagnosis, contamination, mixed cultures, ASB, a UTI could easily be mis-classified as non-UTI or non-UTI as UTI. Exposure or risk factor status could also be mis-classified, for example fever, with the large variation in definition and use of different instruments with varying levels of accuracy. The key question is whether the mis-classification is likely to be associated with the outcome (UTI) or exposure (symptom or risk factor) as this will cause bias. Random misclassification can dilute a true association between an exposure and an outcome.

Confounding

This is when an association between an exposure and an outcome is in fact due to a third factor which is associated with both the exposure and outcome.

This is less of a consideration in the interpretation of incidence and prevalence studies. However, it is important when considering whether particular symptoms and signs are predictive of or associated with UTI. For example, if it was found that diarrhoea was

predictive of UTI, this could be due to the confounding effect of contamination. Diarrhoea may make contamination of the urine sample more likely and contamination of the urine sample might make the diagnosis of UTI (positive culture) more likely.

Background summary

UTI in children is important because it causes acute suffering and it has been linked with long-term complications including renal scarring, hypertension and renal failure. Although there remains some doubt about the strength of the associations with hypertension and renal failure, there is significant evidence for the association of UTI with renal scarring. This association has been seen in children with and without VUR. There is limited evidence that prompt treatment of UTI with antibiotics reduces the risk of renal scarring. There has been a recent change in the emphasis of treating children with UTI away from invasive investigations and prophylactic antibiotics towards the prompt diagnosis and treatment of UTI. This is likely to be both more effective and less costly for the NHS.[144]

There is evidence that UTI in children is under-diagnosed with many cases missed, particularly in primary care. This appears to be largely due to insufficient urine sampling, presumably due to low levels of suspicion by clinicians and the non-specific nature of presenting symptoms and signs. The widespread belief and emphasis in current guidelines that UTI is unlikely if fever is not present or if there is evidence of an alternative source of infection may be contributing to the problem. Practical problems associated with obtaining urine samples in young children are also likely to compound the low levels of urine sampling.

We do not know how significant the problem is as we do not know the true prevalence of UTI in presenting ill children. This is because published studies generally have not systematically sampled urine from children. Those that have were rarely in the UK, usually in emergency departments, and often had highly selective inclusion criteria, for example fever >38^{o}C and only very young infants. Without knowing the prevalence of UTI, it is also difficult to advise on levels of urine sampling in primary care.

There are no clear symptoms and signs which predict UTI in children, the diagnostic test (urine culture) is far from perfect and it takes 2-3 days for the treating primary care clinician to get the results. Studies reporting the symptoms and signs of UTI in children tend to be

secondary care studies and very few have systematic sampling of ill children. Almost all studies exclude children without fever.

Research questions

My main research question is: What is the prevalence of UTI in acutely ill children under five years old presenting in primary care?

My other research questions are:

- What clinical features (symptoms, signs and risk factors) predict UTIs in children?
- Which children should have their urine sampled?
- What are the clinical outcomes for children diagnosed with UTI in primary care?

Aims of research

Primary aim

- To determine the prevalence of UTI in young children (under five) presenting with an acute illness (<28 days) in primary care.

Secondary aims

- Identify the sensitivity, specificity and predictive values of clinical features and point-of-care dipstick urine tests in predicting UTIs in children in primary care.
- Identify clinical outcomes for children diagnosed with UTI in primary care.

Research objectives

1. Conduct a systematic review of the literature concerning the prevalence and incidence of UTI in children in primary care.
2. Conduct a pilot study to determine the feasibility of recruiting and obtaining urine samples from ill children in primary care.
3. Conduct a study to determine the prevalence of UTI (defined as $>10^5$ organisms/ml of urine) in children aged before their fifth birthday presenting to primary care with an acute illness of less than or equal to 28 days duration.
4. Determine the predictive values of symptoms, signs, risk factors and point of care dipstick tests in predicting positive urine culture (UTI) in urine samples systematically obtained from acutely ill children in primary care.

5. Develop a decision support system and sampling strategy for use in primary care for the diagnosis of UTI in children.
6. Describe hospital referral, hospital investigation, re-consultation in primary care, and further UTI rates at 6 months for children found to have UTI at initial consultation compared with those without UTI.

Chapter 2: Systematic review and meta-analysis
The prevalence of UTI in acutely ill children less than five years old presenting in primary care

Headline: This systematic review was of studies reporting the prevalence of UTI in children consulting in primary care (including A&E) when urine was systematically sampled. Twenty-one studies were finally included in the review and meta-analysis. The pooled estimate for prevalence in febrile children less than three month old was 7.0%. The pooled prevalence for older children (up to five years old) was 8.0%. There was a high level of heterogeneity in the included studies. Most of the studies were set in Emergency Departments (ED) in the USA; and most only included febrile children. This pooled prevalence may not be representative of acutely ill children (not necessarily febrile) consulting in UK general practice.

Background

In chapter one, I discussed the difficulties of diagnosing UTI in children, and the evidence which suggests that many UTIs are missed, particularly in primary care. As a GP, I want to know what the likelihood of UTI is in an acutely ill child consulting at my surgery, i.e. the prevalence of UTI in this population of children. In this chapter I am going to present the results of a systematic review of the literature which I carried out to try to determine this.

There are wide variations in the reported rates of UTI in children. Most studies report the *incidence* of UTI as determined from laboratory samples which have been requested by clinicians who suspect UTI to be present. As I discussed in chapter one, we cannot rely on urine sampling based on clinician suspicion to determine an accurate prevalence of UTI as children with non-specific symptoms will be excluded from urine sampling. The main aim of this systematic review was to identify the prevalence of UTI in acutely ill children less than five years old presenting in primary care. To do that the objectives included searching for and only including studies which had aimed to systematically sample urine from the study population rather than sampling urine according to clinician suspicion of UTI.

There are a number of published reports from settings where urine sampling *is* more systematic, for example in neonatal and paediatric hospital wards where children have been

admitted for serious illness. However, children admitted to hospital are likely to be different from acutely ill children presenting to their GP and the results are unlikely to be generalisable to routine primary care. Children in hospital are usually much more seriously ill and the proportion of these children who have UTI may not be the same as the proportion with UTI in a primary care setting. On an initial search, there seemed to be very few studies conducted in general practice, but several studies in A&E departments. Although the children who present to A&E may be different from children who attend a GP surgery, this is a primary care setting where any patient can consult with an illness, unlike children admitted to hospital who have already been assessed by a doctor. I decided to conduct a systematic search for studies which had systematically sampled urine from children in a primary care setting, including A&E departments.

I found two previous systematic reviews of prevalence of UTI in children, one by Downs (1999) and another by Shaikh and colleagues in 2008.[145 146] Although it was used as part of a quality rating of primary studies in Shaikh et al's review, neither of these systematic reviews excluded studies which had not systematically sampled urine. Ten of the eighteen studies in Shaikh's review had not attempted to systematically sample urine, including two of the largest studies. [77 147]

Aim

The aim of this chapter was to conduct a systematic review of the literature to determine the reported prevalence of UTI in children under the age of five presenting in primary care with an acute illness *when the goal was to systematically sample urine* (rather than sample according to symptoms and signs or clinician suspicion), and to calculate a pooled prevalence of UTI if this was possible.

Method

I developed a search strategy using text words and MeSH terms (Figure 2.1). The MeSH terms were used to search each of the databases with this function and terms exploded when relevant. Text searches for words were searched using the '.mp' term which is the widest search option for text. These searches were then combined. I discussed the search strategy with supervisors and with one of the librarians specialising in systematic reviews. I performed pilot searches and checked important papers were being picked up by the search strategy. All the important papers which were known to me at the time were picked up by the

initial search. The databases searched were Medline, Medline-in-process, EMBASE, Cochrane Database for Systematic Reviews (DARE), HMIC, British Nursing Index, CINAHL and Web of Science. The original search was performed in July 2009 and updated in October 2012 (15/10/12). Reference lists of review articles and guideline documents were also searched for potentially relevant papers.

Figure 2.1: Search strategy

(urinary tract infection* or UTI or cystitis or pyelonephritis).mp text words and MeSH terms

AND

(child* or paediatric* or pediatric* or infant* or newborn* or baby or babies or neonat* or toddler*).mp. text words and MeSH terms

AND

(primary care or primary health care or general practice* or family * or (accident and emergency) or emergency medicine or community health centre* or family medicine or family physician or ambulatory or unscheduled or paediatric assessment unit* or walk in centre* or prevalence).mp. text words and MeSH terms.

Methods of review

Selection of studies

I assessed the titles and abstracts of all of the papers found with this search, against the inclusion and exclusion criteria (figure 2.2). Abstracts of identified studies were stored in Endnote and duplicates removed. A sample of 10% of the titles and abstracts were also assessed by one of my supervisors (Professor Edwards). We marked each abstract as a definite inclusion, probable inclusion, probable exclusion or definite exclusion according to the above inclusion and exclusion criteria. The full text article was obtained for all of those which were not definitely excluded on the review of abstracts. We had near complete agreement at this stage. On the few where we disagreed the full paper was obtained. As we had nearly complete agreement on this first stage, I assessed the remaining 90% of abstracts and titles myself. Both my supervisor and I assessed all of the full papers which were

indentified from the first stage and marked them as definite inclusion, definite exclusion, possible inclusion or possible exclusion. Where we had disagreement and for the possible inclusion and possible exclusion categories, we discussed the papers in more detail to reach a consensus decision. There were five papers identified from the first stage as possibly eligible for review of the full article which were subsequently excluded due to the full article being written in a language which was not English.

Figure 2.2: Inclusion and exclusion criteria

Criteria for including studies

1) Studies must include children under five years old
    - Studies of children over the age of five included if prevalence is reported separately for under fives.
2) Children should be presenting in primary care (include general practices, A&E, Out of hours co-operatives and walk-in centres).
3) UTI must be determined by microbiological culture. Studies using a definition of UTI of $>10^5$ organisms/ml for clean catch or bag or pad samples and $>10^4$ organisms/ml for catheter samples and $>10^2$organisms/ml or $>10^3$ organisms/ml for suprapubic (SPA) samples will be included.
4) Must involve systematic sampling (sampling urine from all children in the study population rather than only sampling urine from those children that the clinician suspects of having UTI).

Studies reporting prevalence, point prevalence, cross-sectional prevalence and incidence are all included.

Exclusion criteria

1) Papers in languages other than English
2) Studies from developing countries
3) Studies of asymptomatic children
4) Studies in secondary care
5) Case series, case reports and case-control studies except where nested as part of a cohort study
6) Studies which only include very specific groups of children e.g. with spina bifida, diabetes, long-term catheters, structural abnormalities of the urinary tract.

Data extraction

From studies which met the inclusion criteria I extracted the data for the age range of children in the study, the sample size of the population under five years old, the country, the setting (e.g. general practice/A&E), the inclusion criteria for the study (particularly the temperature), the proportion of the study population whose urine was sampled, the method of urine sampling, the definition of UTI used and the prevalence of UTI.

Statistical analysis

Data were entered into EXCEL (version 2007). Confidence intervals given by individual studies were not used. Confidence intervals were calculated using raw data given in papers and using a method appropriate for proportions close to zero.[148] A pooled UTI prevalence was estimated and Forest plots drawn using the calculations and spreadsheets provided by Neyeloff et al.[149] However, they calculated confidence intervals using the standard method which is less suitable for proportions close to zero, so I calculated confidence intervals using a more appropriate method instead of using those given by the spreadsheet (as above).[148] Neyeloff's spreadsheet was also used to calculate the Q and I^2 statistics to assess heterogeneity of papers. Due to significant heterogeneity, a random-effects model was used to calculate the pooled estimate of prevalence and associated confidence intervals.[149] Sensitivity analyses were performed excluding one study with an outlying prevalence and excluding studies with less clear or lower diagnostic thresholds for UTI.

Results

From the initial search, 4713 articles were found and 148 full text articles were reviewed. Nineteen articles met all the inclusion criteria. From the updated search, a further 55 articles were identified and a further four full text articles reviewed. Two were subsequently included, one of which was the paper reporting my pilot study.[150] Twenty-one studies were included. The included studies are shown in Tables 2.6 and 2.7. I considered the studies in two groups. Fifteen studies were of children aged three months old or under (Group A; table 2.6) and six studies included children up to the age of five years old (Group B; Table 2.7). Tables 2.8 and 2.9 give further details including inclusion criteria, urine sampling method, the definition of UTI used, the sample number and the prevalence of UTI for included studies. Tables of summaries of studies which were considered more closely due to the

possibility of overlapping datasets or where only some of the data were used are presented in Appendix 2.1.

Table 2.6: Included studies: Group A: Studies of children ≤ 3 months old

Lead author	Year	Country	Setting	Study design	Age of children
Baker[151]	1993	USA	Paediatric ED	Prospective	29-56 days
Bonadio[152]	1991	USA	Paediatric ED	Prosepective	30-60 days
Bonadio (i)[65]	1993	USA	Paediatric ED	Prosepective	0-8 weeks
Bonadio (ii)[66]	1993	USA	Paediatric ED	Retrospective	0-8 weeks
Bonadio[67]	1994	USA	Paediatric ED	Retrospective	8-12 weeks
Crain[63]	1990	USA	Paediatric ED	Prospective	0-8 weeks
Dayan[100]	2002	USA	Paediatric ED	Prospective	1-60 days
Herr[70]	2001	USA	Paediatric ED	Retrospective	0-60 days
Hoberman[48]	1993	USA	Paedatric ED	Prospective	0-2 months
Krober[61]	1985	USA	Army medical centre	Prospective	0-3 months
Levine[101]	2004	USA	Paediatric ED	Prospective	0-60 days
Lin[102]	2000	Taiwan	ED or outpatient clinic	Prospective	0-8 weeks
Maniaci[71]	2008	USA	Paediatric ED	Prospective	0-90 days
Schwartz[103]	2009	Israel	Paediatric ED	Retrospective	0-28 days
Stanley[153]	2005	USA	Paediatric ED	Retrospective	0-3 months

Table 2.7: Included studies: Group B: Studies of children up to 5 years old

Lead author	Year	Country	Setting	Study design	Age of children
Hsiao[73]	2006	USA	Paediatric ED	Prospective	57-180 days
Manzano[154]	2010	Canada	Paediatric ED	Prospective	1-36 months
North[60]	1963	USA	ED or outpatient clinic	Prospective	<13 years*
O'Brien[150]	2011	UK	General practice	Prospective	<5 years
Shaw (i)[68]	1998	USA	Paediatric ED	Prospective	Boys <1 year Girls <2 years
Torrijos[83]	1989	USA	ED or outpatient clinic	Prospective	Unclear. Mean age UTI group= 22.6 months and non-UTI group= 28 months

* Data for <5 year olds presented

Table 2.8: Inclusion criteria, urine sampling method, UTI definition, sample size and prevalence given in included studies for group A

Lead author and date	Temp	Other inclusion criteria	Urine sampling method	UTI definition	Sample size	Number urines samples (%)	Prevalence
Baker 1993	Rectal temp $\geq$38.2^{o}C	-	Catheter	Unclear: "considered negative or contaminated if <10^3cfu/ml single organism or 10^5 with 3 or more colony types present and none predominant"	747	747 (100%)	24 (3.2%)
Bonadio 1991	Rectal temp >38.0^{o}C	-	Not stated	Not stated	161	161 (100%)	7 (4.3%)
Bonadio (i) 1993	Rectal temp $\geq$38.0^{o}C recorded at triage or $\geq$100.4^{o}F recorded by a caretaker	Excluded children who were "culture negative for bacterial pathogens & had received antibiotic therapy within 72 hours"	Catheter	$\geq10^4$ cfu/ml single species	233	233 (100%)	7 (3.0%)
Bonadio (ii) 1993	Rectal temp $\geq$38.0^{o}C recorded at triage or $\geq$100.4^{o}F recorded by a caretaker	-	Catheter or SPA	$\geq10^4$ cfu/ml single organism by catheter or $\geq10^3$cfu/ml by SPA	1130	1130 (100%)	39 (3.5%)
Bonadio 1994	Rectal temp $\geq$38.0^{o}C	Excluded 1) if "culture negative for bacterial pathogens & had antibiotics within 72 hrs presentation" 2) if received antipyretic medications within 4 hours of presentation	Catheter	$\geq10^4$ cfu/ml single organism	367	321 (90%)	17/321 (5.3%) but they state 4.8%
Crain 1990	$\geq$38.1^{o}C	-	Bag, catheter or SPA	$\geq10^4$pure growth for bag or catheter specs. $\geq10^2$ for SPA	442	429 (97%)	33/429 (7.7%) but they state /442 =7.5%

Lead author and date	Temp	Other inclusion criteria	Urine sampling method	UTI definition	Sample size	Number urines samples (%)	Prevalence
Dayan 2002	Reported or recorded rectal temp $\geq$38.0^{o}C	Excluded if had received antibiotics within 48 hrs of evaluation	Catheter or SPA	$\geq 10^4$growth single uropathogen for catheter. $\geq 10^3$ for SPA	235	232 (98.7%)	27/232 (11.6%)
Herr 2001	$\geq$38^{o}C	-	Catheter	>5x10^4 cfu/ml single organism.	434	404 (93%)	25/404 (6.2%)
Hoberman 1993	Rectal temp $\geq$38.3^{o}C recorded in the ED or a hx of rectal temp $\geq$38.3^{o}C or axillary temp $\geq$37.4 ^{o}C recorded within previous 24 hrs	Excluded children who had received antibiotics or had catheterisation in the previous 48hrs	Catheter	$\geq 10^4$ cfu/ml single organism	306	100% for 306 $\leq$2 mth olds	14/306 (4.6%) in <2 mths
Krober 1985	Rectal $\geq$38^{o}C	-	Catheter	>10^4 cfu/ml	182	182 (100%)	20 (11%)
Levine 2004	$\geq$38.0^{o}C	Excluded if had had antibiotics within 48 hrs of presentation	Catheter or SPA	$\geq$5 x 10^4cfu/ml of single pathogen or $\geq 10^4$cfu/ml & positive urinalysis for catheter specs or $\geq 10^3$cfu/ml for SPA	1248	1227 (98%)	112/1227 (9.1%)
Lin 2000	Rectal temp >38.0^{o}C	Inclusion limited to infants where >5mls urine was obtained from single SPA	SPA	$\geq$100 cfu/ml of a single urinary pathogen	162	162 (100%)	22/162 (13.6%)
Maniaci 2008	Temp $\geq$38^{o}C	Excluded if immunodefieincy or chronic disease, focal bacterial infection (apart from otitis media)VUR, surgery in previous 7 days, immunisation or antibiotics within 48 hrs.	Catheter	$\geq 5x10^4$ cfu/ml single organism or 10^4- 4.9x10^4 + positive urinalysis ($\geq$5 WBC microscopy or leuk & nitrite + on dip)	874	97% (848)	24/848 (2.8%)

Lead author and date	Temp	Other inclusion criteria	Urine sampling method	UTI definition	Sample size	Number urines samples (%)	Prevalence
Schwartz 2009	Rectal $\geq$38.0^{o}C	Excluded neonates with <37/40 gestation, prior hospitalisation or receipt of antibiotics, known chronic disease, source of infection apparent on physical examination other than otitis media	SPA or catheter	Any growth of a single known uropathogen, isolated growth of >10^3 cfu/ml of single skin bacteria or >10^2 cfu/ml of at least one known uropathogen if 2 bacteria were isolated and >10^4 of at least 1 uropathogen if 3 organisms were isolated	463	449 (97%)	82/449 (18.3%)
Stanley 2005	$\geq$40.0^{o}C	Excluded children with underlying medical conditions, known immunodeficiency, or those who received antibiotics within 48 hrs of ED presentation.	Catheter or SPA	$\geq10^4$ pure cfu/ml from catheter or $\geq10^3$ from SPA	92	92/92 (100%) had urine cultures	25/92 (27%)

Table 2.9: Inclusion criteria, urine sampling method, UTI definition, sample size and prevalence given in included studies for group B

Lead author and date	Temp	Other inclusion criteria	Urine sampling method	UTI definition	Sample size	Number urines samples (%)	Prevalence
Hsiao 2006	Rectal temp >37.9°C	-	Catheter in all but 2 who had SPA	$>10^4$ cfu/ml single organism	429	429 (100%)	41/429 (9.6%)
Manzano 2010	Rectal temp >38°C	No source of infection after careful history, examination and blood test. Excluded if immunodeficiency or on antibiotics	Catheter or SPA	Any growth on SPA or $\geq 10^5$cfu/ml single pathogen on catheter sample	384	Not stated. Assume 384 (100%)	56/384 (14.6%)
North 1963	≥38°C	'undiagnosed and untreated febrile illness'	Catheter or clean catch	$>10^5$ bacteria/ml	63 <5 yr olds	63	2/63 (3.2%)
O'Brien 2011	any	Excluded if known urinary tract abnormalities, on long-term antibiotics or immunosuppressant medication	Clean catch or nappy pad	$\geq 10^5$ cfu/ml pure/predominant growth	99	71 (72%)	3/71 (4.2%)
Shaw (i) 1998	≥38.5°C	Excluded if taking antibiotics, immunosuppressed or had a definite source of fever on examination*	Catheter	$\geq 10^4$cfu/ml single urinary tract pathogen	2908	2411 (83%)	80/2411 (3.3%)
Torrijos 1989	any	Otitis media (clinical findings of redness, absence of light reflex in TM, bulging and rupture +/- discharge or fever and symptoms or URTI)	Clean catch, MSU or bag	$\geq 10^5$ cfu/ml pure culture	106	106 (100%)	17/106 (16.0%)

* Excluded children with meningitis, pneumonia, septic arthritis, cellulitis, adenitis, osteomyelitis, perf otitis media with exudate, scarlet fever, varicella, coxsackie diseae, measles, herpetic stomatitis, bronchiolitis, Kawasaki disease and HSP but included URTI, gasroenteritis, viral exanthema and otitis media

There was variation between studies in both groups A and B. Although most studies required fever to be present, this varied from $\geq$37.4 ^{o}C axillary to $\geq$40.0 ^{o}C rectal temperature. Some studies allowed a fever recorded by a care-giver rather than at the time of recruitment.[48 61 65 66 100] All but two of the studies were conducted in the USA. The others were conducted in Taiwan and Israel.[102 103] The studies conducted in the USA and Israel had high levels of circumcision. Some studies excluded children with a clear source of infection.[60 68 71 103] One study only included children with otitis media.[83] Most excluded children who had received antibiotic treatment recently,[48 65 67 68 71 100 101 153 154] and one excluded children who had received antipyretic medication recently.[67] Urine samples were usually taken using a catheter or SPA and the diagnosis of UTI was usually $\geq 10^4$cfu/ml pure predominant growth from a catheter sample or $\geq 10^3$cfu/ml pure or predominant growth from a SPA sample, although there was some variation in the definitions used (Baker $\geq 10^3$cfu/ml from a catheter sample[151]; Bonadio 1991 did not clearly state the counts used[152]; Crain & Lin $\geq 10^2$cfu/ml for SPA samples[63 102]; Herr $\geq 5x10^4$cfu/ml[70]; Maniaci & Levine $\geq 5x10^4$cfu/ml or $\geq 1x10^4$cfu/ml & positive urinalysis[71 101]). Clearly, different definitions of UTI will result in different prevalence rates.

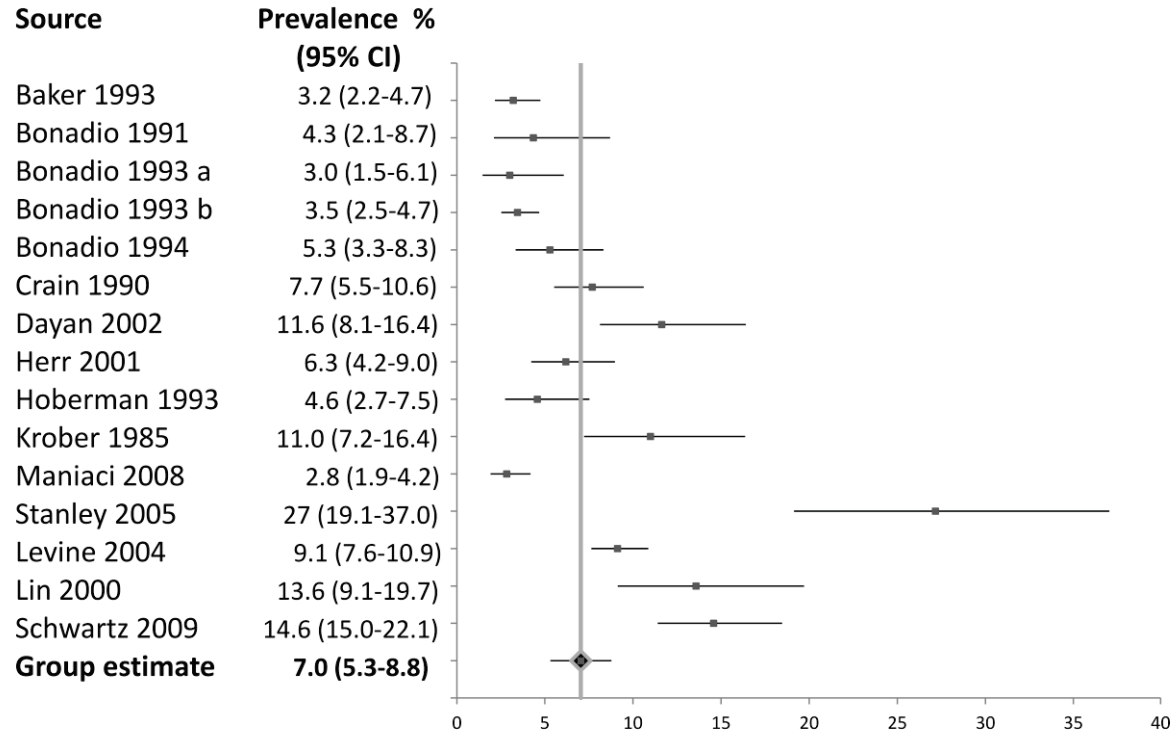
Most studies specified that urine was systematically sampled from all children as an inherent part of the study method. Some did not specifically state this as part of the research study method, but stated that it was the protocol or clinical guideline for the paediatric department.[68 70 71] In one case, 93% urine retrieval was achieved;[70] in another, 97%[71]; and in another 83%.[68]

Some studies describe 100% urine retrieval. Although this may be possible, especially in paediatric emergency departments where obtaining urine samples, often using a catheter or SPA may be standard, it does raise suspicion that the study population was selected on the basis of a urine sample being provided as it seems unlikely that a urine sample will be obtained in every case in which it is requested or attempted.

I calculated a pooled prevalence estimate for the fifteen studies of children aged three months or less as the methods and inclusion criteria of these studies seemed to be similar enough to justify this (Figure 2.3). They were all of children within a narrow age range; both male and female children were included; all but one[61] were recruited from Paediatric Emergency

Departments; all were included only if they had fever, in most cases approximately 38°C. A Forest plot with the pooled estimate is shown on Figure 2.3.

Figure 2.3: UTI prevalence (squares), 95% confidence intervals (lines) and pooled prevalence (diamond) in Group A studies



NB. Size of squares is not proportional to the sample size of the study

$Q=124.31$; $I^2=88.74$

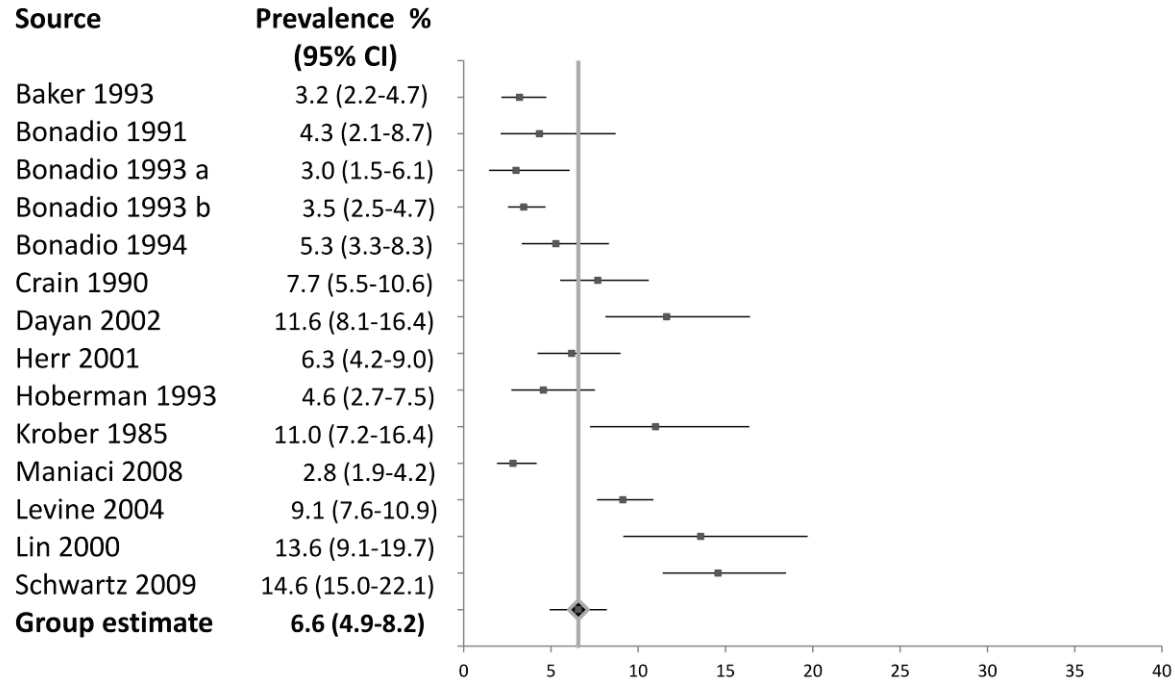
X^2 test with 14 df $p<0.001$

Sensitivity analysis

The prevalence found by Stanley was much higher than those found in the other studies in group A (see Figure 2.3).[153] The data included from this study was only part of the complete dataset as for the majority of the sample the urine sampling did not appear to be systematic with only 6% of the total dataset (316/5273) having their urine sampled. The paper's focus was hyperpyrexia, and those infants with a temperature of >40°C all had their urine sampled. However, the sample was small (n=92) and required a higher inclusion temperature than the other included studies. Therefore I calculated a pooled prevalence and Forest plot excluding the study by Stanley (Figure 2.4).[153] Excluding this study gave a pooled prevalence of 6.6%. I

also calculated a pooled prevalence excluding the five studies where the definition of UTI was less clear[103 151 152] or used the lower threshold (>10^2 cfu/ml or less) for SPA samples.[63 102] This resulted in a pooled prevalence of 5.9.

Figure 2.4: UTI prevalence (squares), 95% confidence intervals (lines) and pooled prevalence (diamond) for Group A studies (included children <3 months with fever) excluding the study by Stanley.

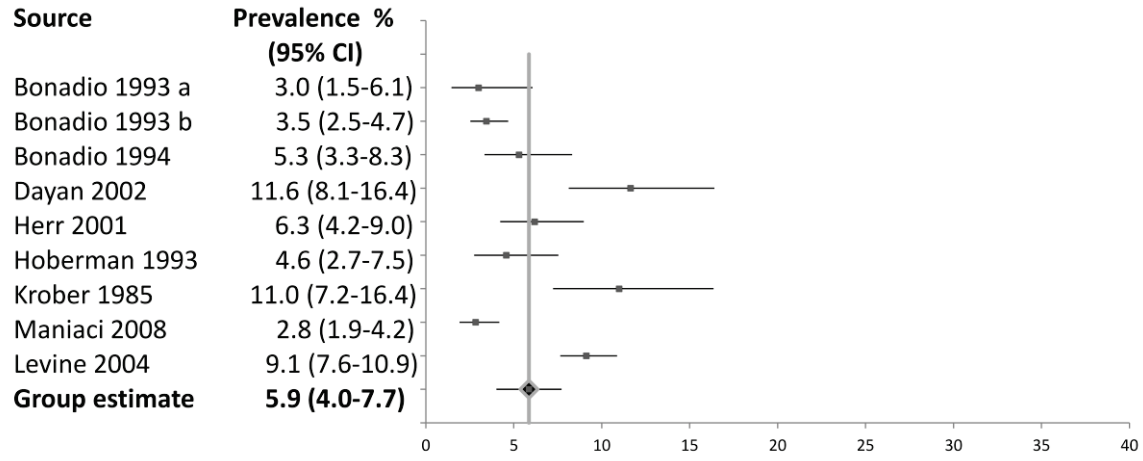


NB. Size of squares is not proportional to the sample size of the study

$Q=107.28$; $I^2=87.88$

X^2 test with 13 df $p<0.001$

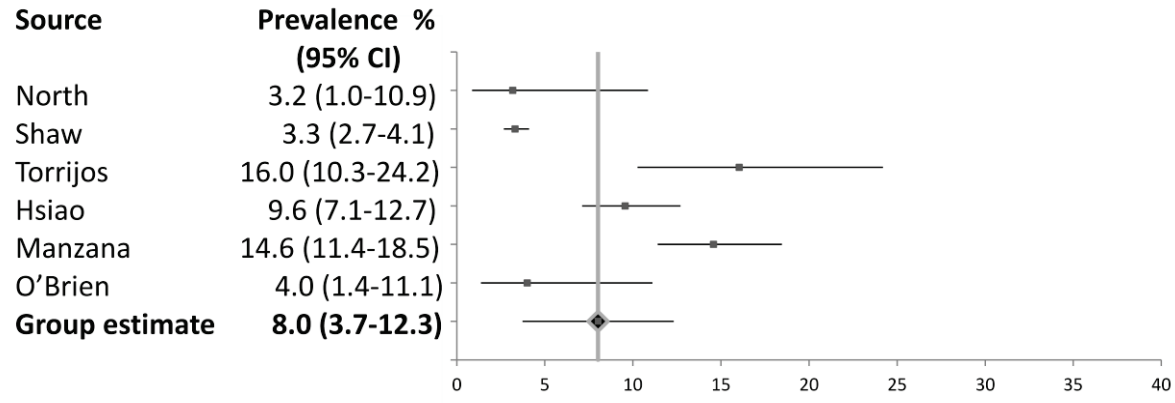
Figure 2.5: UTI prevalence of Group A studies with pooled estimate excluding the study by Stanley and the five studies with variation in UTI definition



Q=61.8
I^2=87.1

I calculated a pooled prevalence estimate for the six studies of older children (aged between three months and five years old). However, these studies had greater variation in methods. Figure 2.6 shows the associated Forest plot and pooled estimate.

Figure 2.6: UTI prevalence (squares) and 95% confidence intervals (lines) for Group B studies (included children up to five years old)



NB. Size of squares is not proportional to the sample size of the study

Q=56.3; I^2=91.1

X^2 test with 5 df p<0.001

The Q and I^2 statistics are measures of heterogeneity. Both were high (124.3 and 88.7 respectively) for the fifteen studies for children aged 3 months or less (Group A; figure 2.3); and remained high when the outlying study was excluded (Q=107.3; I^2=87.9; figure 2.4). These statistics were high for the six studies for older children (Group B; Q=56.3; I^2=91.1; figure 2.6). Group B studies seemed to vary more methodologically than Group A, with greater variation in age, temperature, inclusion and exclusion criteria. The Q statistic for Group B studies was lower than for the Group A studies, but the I^2 was 91.1 indicating that 91.1% of the variation in prevalence was due to the heterogeneity of studies.

It is debatable whether the studies are too heterogeneous to present a pooled estimate, but it is not clear at what point the heterogeneity is thought to be too high. It is most important to understand the cause of the heterogeneity.[155 156] The I^2 value represents the percentage of the total variation across studies which is due to the heterogeneity of studies rather than chance alone.[155] Therefore, an I^2 of 88.7 (for Group A) suggests that 88.7% of the variation in my meta-analysis is due to the heterogeneity of the studies rather than chance. The pooled estimate is therefore more like an average of the prevalence found in the studies rather than the best estimate of the true population prevalence.

Shaikh et al do not give their values for Q or I^2, although they do give the p-value for the chi-squared test using the Q statistic.[145] They found it to be highly significant ($p<0.01$), indicating significant heterogeneity. I calculated the Q and I^2 statistics for their analysis using the Neyeloff spreadsheet and found them to be 162.2 and 92.0 respectively.[149]

Discussion

Summary of results

A total of 4768 articles were found using the search strategy and 152 full text articles were reviewed. Twenty-one studies met all the inclusion criteria.

The pooled estimate for the prevalence of UTI in febrile children less than three months old was approximately 7.0%. Excluding studies with less stringent definition criteria resulted in a pooled prevalence of 5.9% for febrile children less than three months old. The pooled estimate for the prevalence of UTI in children up to the age of five years old was 8.0%. Chi^2

tests for heterogeneity were strongly significant with p-values of <0.01 and high I^2 values for both groups of studies, signifying high levels of heterogeneity.

Strengths and weaknesses

Strengths

This was a systematic review of the literature involving two researchers selecting studies according to pre-determined inclusion and exclusion criteria. This method reduces the chance of selection bias in the meta-analysis. Systematic urine sampling rather than clinician-suspicion led urine sampling was one of the key inclusion criteria. This ensures that the UTI prevalence is a true representation of the prevalence in the study populations, and therefore a more accurate estimate of the population prevalence, rather than the prevalence of UTI among a clinician selected sub-set of the study population.

Weaknesses

Non-English articles were not included in the review. The effect of publication bias was not assessed. Although it is possible that journals may find a higher prevalence more attractive, I felt that publication bias was unlikely to be a significant factor, where, unlike an intervention study, there are no positive or negative findings.

The main weakness of the meta-analysis is the heterogeneity of studies. The high level of heterogeneity calls into question the validity of the pooled estimates, which are therefore more like an average of the findings of a variety of studies rather than a more accurate representation of the true population prevalence.

Context/other studies

My findings are very similar to the findings of Shaikh et al, despite different inclusion and exclusion criteria and subsequently different studies included in my meta-analysis compared with theirs.

Even if the pooled prevalence estimate is representative of the true population prevalence, the populations in these studies are quite different from the population of presenting ill children in UK primary care and the estimate is unlikely to be generalisable to the UK population.

Nearly all the studies were from the USA. The ethnic makeup of the USA is different from the UK, with approximately 72% of the population White and approximately 13% Black in the USA compared with 91% White and 2% Black in the UK.[157] Some of the studies which gave a description of the race of participants had even greater differences in ethnicity from the UK, for example Shaw et al described 84% of their study population as African American.[68] Ethnicity has been found to be associated with UTI, with most studies finding that UTI is more common in White children than African American children. A high proportion of African American children in the studies included in the meta-analysis may underestimate the prevalence for a predominantly white UK population.

There are much higher levels of circumcision in the USA compared with the UK (approximately 80% in USA; 3% in UK).[158] Being circumcised has been associated with a lower risk of UTI compared with uncircumcised boys (odds ratio of 0.1).[159] Some of the studies included in my systematic review stated the proportion of boys who were circumcised. Hoberman et al found 98% of boys in their study population were circumcised[48]; Shaw found 87%[68]; Hsiao 72% and Schwartz (Israel) found 97%.[103] A high proportion of circumcised boys in these studies may underestimate the prevalence for a predominantly uncircumcised UK population.

All of the studies but two included only children who were febrile.[83 150] In most cases, a temperature of at least 38^{o}C was required. In addition to the problem of defining fever and different methods of measurement, as I discussed in chapter one, fever is not always present in a UTI and excluding non-febrile children may miss some cases of UTI. This could result in studies including only febrile children to underestimate UTI prevalence. However, if UTI is more common in children with fever, then excluding those without fever may cause an overestimation of UTI prevalence as a proportion of the study population.

Implications for policy, practice and further research

My pilot study was the only UK based primary care study of UTI prevalence using systematic urine sampling identified by my systematic review.[150] It was also the only study using urine sampling methods suitable in general practice and including all acutely ill children irrespective of potential alternative sources of infection or temperature. However, the sample size was very small and confidence intervals were wide.

Given the high proportion of Whites and un-circumcised boys in the UK compared with the populations studied in the majority of papers included in this review, the prevalence of UTI in acutely ill children in the UK may be higher than that found in the studies presented here. On the other hand, with selective inclusion criteria such as high temperature or absence of alternative sources of infection, and recruitment predominantly from paediatric emergency departments, the prevalences reported in the studies in this review may be higher than that in the population of acutely ill children presenting in UK general practice.

If the true prevalence in acutely ill children less than five years old is 7-8% (or higher), this has significant implications for clinical practice. Substantial increases in urine sampling from ill children may be indicated, perhaps in all acutely ill children. Evaluation of the cost-effectiveness of such approaches would need to be established.

Given the heterogeneity of included studies and the differences between the populations included in these studies and my target population, I am not confident that the pooled prevalence found in this systematic review is representative of children less than five years old with an acute illness presenting in UK primary care. Further research is needed to identify the prevalence in this population.

Conclusion

This systematic review and meta-analysis highlights the need for a large prospective study of UTI prevalence, with systematic urine sampling, in acutely ill children presenting in UK general practice.

Chapter 3: Pilot Study

Headline: The pilot study showed that it was feasible to recruit children less than five years old from general practices and obtain urine samples from them. A total of 99 children were recruited from four general practices, with full laboratory results in 72%. The prevalence of UTI was 4% (95% CI: 1%-18%). The pilot study helped to secure funding and informed the study design of the main study.

Background

Aims and objectives

Before undertaking a large cohort study, a pilot study was needed to determine whether it would be possible to recruit young children and obtain urine samples in GP surgeries.

Need for the pilot study

Before a grant was awarded by WORD for the study, I had applied to several fellowship schemes for funding for a PhD based on this study. Reviewers of the fellowship applications gave positive feedback but expressed concerns about recruiting young children from primary care. Other studies had apparently had significant difficulties in recruiting febrile children from GP practices. One study in Bristol struggled to recruit children from general practice.[160] The initial target sample for this study was 747. Following recruitment problems, this was revised to 180, with a final sample of 156 achieved. However, this study involved randomisation and required a fever at the time of recruitment of at least 37.8^{o}C. Although the inclusion criteria for my study were broad, including not only febrile children but any acutely ill child, and was only observational, reviewers remained doubtful about the feasibility of recruitment.

It was also unclear how easy it would be for practices to obtain urine samples from all attending ill children. No previous studies had attempted to do this in UK GP surgeries.

I did not know how often urine would *normally* be sampled in children consulting with an acute illness in general practice. I tried to answer this question in Chapter 1 (page 20). I estimated that GPs probably sample urine from acutely ill children in less than 1% of consultations. Although these figures are only an approximation, even allowing for a large

degree of error, these figures do suggest that it is unusual for GPs to obtain a urine sample from an ill child. This suggested that we could face difficulties obtaining urine samples from all acutely ill children in primary care.

Van der Voort et al (1997) sent a questionnaire to GPs concerning UTI in children under two, awareness of guidelines and barriers to diagnosis.[41] They found that GPs reported practical difficulties in obtaining urine samples from young children. These included problems engaging the co-operation of parents, time constraints and availability of equipment.

A pilot study was therefore needed to see if it would be possible to recruit and obtain urine samples from ill children in GP practices. We needed to be sure that it was feasible to do a small study before investing large amounts of time and money for a large study. We also needed to obtain funding to carry out the large study and needed to be able to demonstrate feasibility to potential funders.

Aim

The aim of the pilot study was to determine whether it was feasible to recruit children less than five years old in primary care and obtain urine samples from them.

Objectives

- Recruit 100 children aged under five from GP practices into the study
- Obtain urine samples from all children recruited

Method

Approvals

Ethical approval for the pilot study was obtained from the South East Wales Local Research Ethics Committee (ref no.06/WSE03/117). I submitted an application including both the pilot study and subsequent planned large study, but the Ethics committee only approved the pilot study and requested a further application for the full study once the results of the pilot study were known. Site specific assessment for each of the practices was also carried out by this Ethics Committee. Approval was obtained from Cardiff Local Health Board (LHB) and The Vale of Glamorgan LHB for the practices taking part in the study.

Practice recruitment

Four practices were asked to recruit for the pilot study. These practices were chosen as they were part of a network of research practices, known to have a practice nurse who had previously been involved in research studies. One practice had a nurse employed solely for research purposes who was also able to play a co-ordinating role with the other practices. One of the practices was located in Ely, and the other three in Barry. These practices were chosen for convenience. They had the resources to start the pilot study straight away and with their research experience would be able to give feedback and advice to improve procedures when (if) we progressed to a large study. These practices were not randomly selected and were not representative of all practices in Wales, but the purpose of the pilot study was to see whether it was feasible to recruit children and collect urine samples in selected practices, and hopefully to determine study processes which could then be rolled out to less research-experienced practices for the larger study.

Practices were paid £50 per participant recruited into the study. This was funded by the Department of Primary Care & Public Health. Study equipment was provided to surgeries, including a digital tympanic thermometer which practices could keep following completion of the pilot study. The amount of reimbursement for practices was decided upon after discussion with Professors Butler, Edwards and Hood as well as the research nurses at the practices. The amount of reimbursement was similar to those in other primary care research studies in the Department of Primary Care and Public Health, and reflected the time that it was estimated to take the research nurse and GP to complete the CRF and obtain the urine sample.

Training

Practice nurses and GPs from each of the four practices were invited for training at one of the surgeries. The practice nurse who would be the research lead from each site attended, along with two of the GPs from one of the practices and a healthcare assistant from one of the practices. A further training session was carried out at each of the practices at the start of the study. In three of the practices this was with the practice nurse; in the fourth, this was with the practice nurse and one of the GPs.

In the first training session, I explained the rationale for both the main study and the pilot study; described study procedures in detail and invited comments and discussion on these;

provided study documents which needed to be completed; consent procedures, processes for obtaining urine samples, procedures for data collection and follow-up. Everyone attending was encouraged to participate in discussions and consider how the study would best be run within their own practice environments.

The second training sessions were one-to-one sessions with practice nurses (and a GP in one case). The aim of these sessions was to provide equipment and study documents, to go through the study protocol and documents in detail and how this would be implemented in their practice and to answer any questions.

Participant recruitment

Practices started recruitment in February 2007. Each practice was asked to recruit 25 children, and was encouraged to recruit these as soon as possible, preferably within one month. Each practice was asked to recruit children under the age of five (aged before their fifth birthday), who presented with an acute illness of less than or equal to 28 days duration. Practices were asked to recruit sequential eligible children during times of recruitment. Practices were also asked to keep a log of all eligible children who were approached but did not participate in the study and their reasons for non-participation, and where possible those who were not approached with reasons.

Exclusion criteria

Exclusion criteria were agreed upon after consideration of the main focus of the research, exclusion criteria used in other studies, and following discussion with supervisors. Table 3.2 shows the exclusion criteria. The main aim of the pilot study was to determine feasibility of recruiting young children and obtaining urine samples from them. However, all study procedures, including the inclusion and exclusion criteria, needed to be as similar as possible to those of the intended large study.

Table 3.2: Exclusion criteria

- Previously included in this study
- Past history of urinary tract abnormalities diagnosed with radiological examination (including antenatal ultrasound scan (USS))
- Taking regular, long term antibiotics (for $\geq$ 28 days)
- Taking immunosuppressant medication (chemotherapy for cancer or regular oral steroids ($\geq$ 10mg per day of prednisolone or equivalent for $\geq$ 2 weeks.))

The aim of the research was to determine the prevalence of UTI in ill children seen routinely in general practice, in order to give the treating clinician more information about how likely UTI is, and which symptoms and signs may indicate UTI. I wanted to capture the kind of acutely ill child routinely presenting in primary care, in whom a urine sample would not routinely be taken, and find out the prevalence of UTI in this group, rather than studying groups already known to be at high risk or groups who would already be treated differently, for example immunosuppressed children or those known to have urological abnormalities. At the same time we wanted to be as inclusive as possible to represent the broad spectrum of children seen in GP surgeries.

The inclusion of only children with illnesses of less than 28 days duration was intended to pick up those with an acute illness. We wanted to include 'typical' ill children presenting in GP surgeries, often with only a few days of illness, and also to pick up those who were either not brought to the surgery straight away (perhaps thought to have a self limiting illness by the parents) and those with lingering symptoms. Children with acute illnesses can have symptoms lasting two or three weeks and we did not want to exclude these children.[161] It was difficult to find a clear definition of what constituted an acute illness, and 28 days was decided upon to include most of those with the short term illnesses commonly seen in general practice but exclude those attending for follow-up with chronic illnesses. Twenty eight days has also been used to define the duration for acute illnesses in other published studies.[162]

Data collection

Following consent (Appendix 3.1), clinical history and examination details were recorded on the case record form (CRF) which was completed by practice nurses and clinicians (Appendix 3.2). A urine sample was obtained from each child and the child was managed as normal by the treating clinician. A telephone follow up interview was conducted at three weeks.

Once completed, consent forms and CRFs were returned by fax to a confidential fax machine in a locked room. Alternative methods were considered, including Royal Mail, special delivery or collection by hand. I needed to receive the information straight away so that I could conduct the telephone interviews at three weeks and as the CRFs contained personal and identifiable data we thought that the confidential fax was the best method.

A urine sample was obtained from children either by the clean-catch method or using a urine collection pad inserted in the nappy (Newcastle collection pack). These methods of urine collection were chosen after a review of published studies and current guidelines. Collection of urine by suprapubic aspiration or transurethral catheterisation methods are the most accurate and least likely to give false positive results due to contamination but are invasive and associated with discomfort and distress to children. Both techniques are normally used on seriously ill children and are unsuitable for routine use in primary care. The clean-catch method is the most accurate, non-invasive method in children, and has been found to have reasonably good agreement with urine samples obtained by suprapubic aspiration.[112] Liaw et al (2000) found that pads and bags had similar contamination rates but that parents preferred nappy pads and these were also cheaper.[163] Therefore we decided to use the clean catch method as first choice, and where this was not possible or not acceptable to parents, to use nappy pads.

The urine sample was tested with a urine dipstick (Bayer Multistix GP) by the nurse or healthcare assistant and then sent to the laboratory using the practices' usual transport process. I wanted to include dipstick testing in the large study and so therefore wanted to include it in the pilot study. Using dipsticks as a diagnostic tool, whilst well established in adults, has been controversial in young children. There is a lack of studies using these methods in primary care for young children, and most studies only include children already suspected of having UTI. A systematic review in 2005 concluded that dipsticks may be used to rule out UTI if both Leucocyte esterase (LE) and nitrite were negative, however this was based on an estimated pre-test probability (i.e. prevalence) of UTI of 20%, and would result in a 4% false negative rate.[112] Dipstick testing has not been adequately assessed as a diagnostic test in urine collected systematically from acutely ill children in primary care and the accuracy of the dipstick testing may be different in the population we were planning to study. We do not know the prevalence of UTI in this population but we expected it to be significantly lower than 20%.

Standard microscopy and culture was performed on urine samples and the result sent to the practice in the normal way. Copies of urine results were faxed to the University by practices. All four practices used the same NHS laboratory for processing specimens. It was important to keep the transport, processing, and reporting of urine samples as close as possible to what would normally occur in practices, allowing clinicians to act on results in the normal way. I

wanted this to be primarily an observational study and did not want to influence the management of patients further than we already were by requesting that they obtain a urine sample from all recruited children.

All children were followed up at three weeks with a telephone interview (Appendix 3.3). The aim of this was to determine outcomes of the illness including duration, impact on the family, method of urine sampling and how easy this was, and risk factors for UTI. Three weeks was chosen in the hope that most of the children would have recovered from their illness and so I could collect data on symptom duration but not so long after the event that the parents would have forgotten the details of the illness. If the child had not fully recovered at the time of telephone interview, the continuing symptoms could be recorded using the same table of symptoms used in the CRF at recruitment.

Impact of the illness was also assessed in terms of hospital admissions and other NHS contacts and re-consultations, and parental time off work. Possible risk factors for UTI, and for resistant UTI, were included. It was difficult to decide which potential risk factors and demographics should be collected. As no previous studies had studied UTI diagnosed in this way, I did not know if the risk factors and symptoms would be similar for those with UTI diagnosed in this study. I therefore wanted to include those highlighted as possible factors in the literature, but also include others that may potentially play a part. This decision process took place over time reviewing published studies and following discussions with my supervisors and researchers in the immunology and microbiology fields.

Methods of analysis

Data were entered into SPSS for analysis. The data were cleaned and variables were checked. The main outcome measure was the prevalence of positive culture, with associated confidence intervals. Standard methods for calculating confidence intervals for the population prevalence from a sample prevalence are not accurate when the prevalence (proportion) is low. Therefore I used a method for calculating confidence intervals which is accepted to be more appropriate for proportions close to zero.[148]

Results

Description of sample

Practices recruited children between February and April 2007. The first child was recruited on 5/2/2007 and the last on 20/04/2007, giving a total time to recruit the target of 100 children of nearly 3 months.

Parents of 116 children under the age of five were invited to participate. The parents of seven did not provide consent, three were excluded and the treating GP felt that six were unsuitable. A total of 100 (86.2%) children were both eligible and parents provided consent. In one case, the CRF and consent form subsequently went missing, leaving 99 included in the analysis.

Half (50.5%) of all the children were recruited by the largest practice (EB). Twenty five were recruited by FP, 22 by HS and two by PH. PH dropped out of the study shortly after starting recruitment, having only recruited two children.

The carer consenting for the child to participate in the study was the mother in 86 (86.9%), the father in eight (8.1%) another family member in one (1.0%). In four cases this information was missing.

Overall, 48 (48.5%) participating children were male and 51 were female. The median age was 20 months (IQR 8-32 months). The median age of non-participants was 17 months (IQR 12-35 months). Table 3.3 shows the age and gender of children.

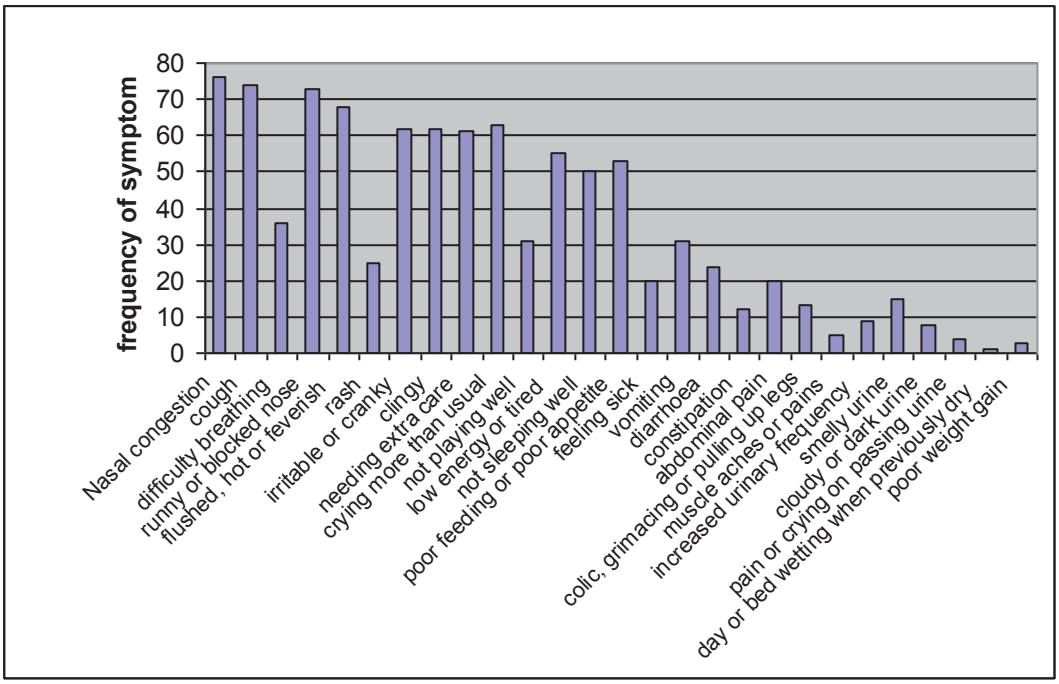
Table 3.3: Age and gender of participating children

Age	Male	Female	Total
0-1 years	18	15	33
1-2 years	9	15	24
2-3 years	12	11	23
3-4 years	4	7	11
4-5 years	5	3	8
All ages	**48**	**51**	**99**

Symptoms and signs

Figure 3.1 shows the number of children with each symptom listed on the CRF. Nasal congestion was the most common presenting symptom with 76% children presenting with this symptom.

Figure 3.1: Frequency of presenting symptoms



Twenty six (26.3%) carers reported that they had measured the temperature at home. The median highest reported temperature was 38^{o}C (IQR 36.9-39.0).

Temperature was recorded in the surgery in 98 (99.0%), pulse rate in 68 (68.7%) and respiratory rate in 61 (61.6%). Temperature was normally distributed with a mean temperature of 36.7^{o}C and a standard deviation of 0.95. Pulse rate and respiratory rate were not normally distributed. The median pulse rate was 119 beats per minute (IQR 100-120). The median respiratory rate was 30 per minute (IQR 20-40).

Parents were asked how sick they thought their child was and how concerned they were about the illness. GPs were asked to give an overall impression of how ill they thought the child was (see CRF, Appendix 3.2). In 41 cases, the parents gave the same score for both questions, and different scores in 58. GPs tended to give lower scores, giving a score lower than both of the parental scores in 61cases.

Laboratory results

Urine samples were obtained in 75 (75.8%). There was a full laboratory result in 71 (71.7%). Urine samples leaked in transit in three (4.0% of urine samples) and were lost in transit in one (1.3%).

A laboratory definition of UTI was met in 3/71 (4.2%; 95% CI 1% - 18%) cases.
A 'borderline', low count (between 10,000 and 100,000 cfu/ml of a single uropathogen) was found in one further (1.4%) case.

Management

One child was admitted to hospital on the same day and two were referred to the hospital (but not admitted on the same day). Sixty eight children were prescribed a medication. This included an oral antibiotic in 28 (41.2%), an antipyretic/analgesic in 23 (33.8%), a topical antibiotic in 8 (11.8%), an antifungal in 4 (5.9%), an antiviral in 2 (2.9%) and other medications (including emollients, steroids, cough medicine) in 26 (38.2%).

In seven (7.1%) children, the working diagnosis recorded by GPs was either 'UTI', 'pyrexia of unknown origin (PUO)' or 'unknown'. None of these turned out to have a UTI. The diagnosis of UTI was not suspected in any of the three children found to have a UTI. In two of the cases found to have a UTI, the GP's working diagnosis was otitis media. In the other case, the working diagnosis was tonsillitis. All three were prescribed amoxicillin.

Telephone follow-up at 3 weeks

Follow-up telephone interviews were completed for 61 (61.6%). The parents reported that the child had completely recovered by the time of interview in 50 (50.5%). The median number of days until recovery in those fully recovered at the time of interview was 7 (IQR 5-14).

Five (5.1%) children had been admitted to hospital. One had been admitted on the same day as the consultation and four were admitted subsequently.

Fourteen (23.0%) were born at full term; 22 (36.1%) were premature and 24 (39.3%) were born postdates. Twenty five (41.0%) were breast fed. Nine (14.8%) mothers had antibiotics during the pregnancy. Twenty four (39.3%) had a family history of UTI.

When asked about urine sampling, 18 (29.5%) reported using the clean catch method and 40 (65.6%) reported using the nappy pad technique. Generally parents found both methods straight forward. Parents were asked to give a score from 0-5 with 0= very difficult and 5= very easy for how easy it was to use whichever method they used to obtain the urine sample. For the clean catch method, the median score was 4 (IQR 3-5), with 14/17 giving a score of $\geq$ 3. For the nappy pad method, the median score was 5 (IQR 3-5), with 35/40 giving a score of $\geq$ 3.

Feedback from practice nurses & telephone follow-up experience

One of the surgeries (PH) dropped out of the study shortly after starting recruitment. The practice nurse leading the study was a nurse practitioner. She was attempting to recruit children and complete all study procedures in addition to consulting with them as their clinician. There was little support or interest from the other clinicians and she was not allocated any extra time for the study. In the other three surgeries, the practice nurses leading study procedures were not the treating clinician that the child was booked in to see. This automatically built in some extra time during which a urine sample was more likely to be obtained. It also meant that there was a break in the study procedures for catching up on normal workload.

Practice nurses reported that the case report forms (CRFs) took less than five minutes to complete, and they became faster once they were more familiar with the questions and the study procedures. Urine collection was also easier than they expected, especially using the nappy pads. The main challenge was getting parents to return urine specimens if they were not obtained in the surgery. All the remaining pilot practices altered their procedures so that potential participants were seen by the practice nurse prior to their booked appointment. After obtaining consent, the urine sampling procedure could be explained and started straight away. Starting the urine sampling as soon as possible increased the likelihood of obtaining a urine sample prior to participants leaving the surgery. Thus urine sampling could be underway whilst the CRF was completed and whilst participants waited for their booked appointment with the clinician. Following their appointment with the clinician, participants would return to the practice nurse for retrieval of the urine sample.

CRFs and consent forms were returned to the University by fax. A number of problems occurred relating to the fax, resulting in changing the procedure part of the way through the pilot study. The front page of the CRF (with patient contact details on for telephone follow-up) and the consent form were faxed and the rest of the CRF was sent by Royal Mail (marked private and confidential).

The telephone follow-up interview usually took less than five minutes to complete. All the parents contacted were happy to answer all the questions. The main challenge was successfully contacting carers. Carers also had some difficulty recalling the duration of symptoms.

Discussion

Discussion of main findings

The pilot study[150] has shown that it is feasible to recruit children under the age of five from primary care and obtain urine samples from them. Parents were generally happy to participate and very few were excluded due to study criteria or by the consulting clinician, with 86% of those approached ultimately participating in the study.

The practice withdrawing from the study resulted in the pilot study taking longer to recruit the children than we had anticipated, however there seemed to be clear reasons for the difficulties, and other practices did not struggle to recruit.

There were equal numbers of male and female children in the study. There were more participants in the younger age groups than in the older (3-5years) groups. The median age of non-participants was similar to that of participants. The numbers of younger children participating in the study is most likely to be due to parents consulting more frequently with younger children, especially infants.

The rate of obtaining urines (75.8%) and leak rate (4.0%) found in the pilot study can be used to inform the sample size for the main study. The prevalence of UTI was found to be 4.2% (95% CI 1-18%). The confidence interval is very wide due to the small sample size. A larger sample size is needed in order to obtain a more accurate prevalence rate.

None of the three children found to have a UTI were suspected of UTI by the GP. All three had been given alternative diagnoses. The numbers in this pilot study were small. However, the finding of UTI in children thought to have an alternative cause of illness has been demonstrated in other studies.[48 68 83 85 164]

Telephone interviews were only successfully completed in 61.6%. This was despite numerous attempts to contact all parents. Sometimes the telephone numbers were incorrect, but more often there were no responses to telephone calls, despite calling at different times of day, and often more than five attempts. When I was successful, the parents were happy to answer the questions and the interviews were completed quickly. When numerous attempts were needed, it was a time consuming part of the study. It was difficult to know whether to leave messages or when to stop trying to contact parents. Generally when I left messages there was no return call (although on one occasion a parent did return my call). I did not want to repeatedly try to contact parents or appear to be putting pressure on them to respond. Also as the time since the initial consultation passed, the parent's memory of their child's illness would be getting worse.

Parents generally reported that obtaining urine samples was straight forward using both methods. However, those using the nappy pads reported this as being easier than those using the clean catch method. Practice nurses also found that the urine sampling was straightforward and easier than they had expected.

Changes to pilot study protocol and study documents

The experience of conducting the pilot study, and the results and feedback from participating nurses, informed the proposed study protocol and documents for the larger study. These are summarised in Table 3.4.

The feedback from the surgery which dropped out was useful in determining how to approach practices for the larger study. It was felt that a smaller number of enthusiastic surgeries with sufficient nursing capacity would be more effective at recruiting than a larger number of less engaged practices or those with lower nursing capacity. It also highlighted the importance of emphasising to practices the need to ensure practice nurses completing study procedures had

the time and support to do this. Therefore larger practices, with two or more nurses were initially approached about the larger study.

Obtaining urine samples from as many of the participants as possible is of paramount importance for an accurate prevalence rate. For the pilot study practices were paid £50 for every child recruited to the study irrespective of whether a urine sample was obtained or not. For the larger study, a reimbursement strategy which reflected the importance and additional time required to obtain a sample may improve the urine sample rate, perhaps with separate fees for enrolment and completion of the urine sample.

The feedback from the nurses that the CRF was quick to complete, coupled with the low rate of completed telephone follow-up interviews led to a significant change in the protocol. Any data needed from all participants would be collected on the CRF, and information only needed on those with a UTI (or borderline result) would be collected by telephone follow-up. This would greatly reduce the workload related to the telephone interviews, would allow more in-depth questions relating to a positive UTI to be asked only of those to whom it was relevant, and would ensure that data needed on all participants were collected systematically. In addition, due to the difficulty some carers were having recalling symptom duration at the telephone follow-up, and as the median duration of symptoms was seven days, it was decided that the telephone follow-up interview in the larger study should be conducted at two weeks rather than three. I also decided that a telephone follow up interview should not be conducted more than four weeks after the initial consultation.

The questions on the pilot study CRF asking the parents how sick they felt their child was and how concerned they were about the current illness were felt by practice nurses to be cumbersome and some reported finding that it was confusing as to how they should be completed. Analysis of these scores was also difficult. This was simplified for the larger study: a five point score instead of 11; clearly defined boxes to tick rather than a line with numbers; and only one question to carers asking how unwell they feel that their child is. One of the reasons for including this in the CRF was to see how the parent's overall impression compared with the GP's overall impression and so the CRF was changed so that the parents and GPs both had the same scoring boxes to complete.

The pilot study has showed that it is feasible to recruit children and obtain urine samples from primary care. Showing this enabled us to secure funding to conduct a large cohort study. The experience of conducting the pilot study and feedback from participating practices informed the development of the protocol and study documents for the larger study.

Table 3.4: Summary of changes made for the main study following the pilot study

Pilot study	**Change for main study**
Assessment of surgery with low recruitment which dropped out (nurse practitioner attempting study procedures within acute clinic)	Target surgeries with sufficient nursing capacity to have a practice nurse completing study procedures.
Urine samples obtained in 76% of recruited children	Reimbursement strategy for practices to be linked with obtaining a urine sample
Only 62% telephone follow-up interviews completed	Collect data required from all participants on the initial CRF. Target telephone follow-up only to those with positive or borderline culture results where more detailed early follow-up data is required
Parents having difficulty remembering symptoms at telephone follow-up interview	Conduct the telephone follow-up interview at two weeks rather than three weeks
Parents having difficulty with the illness scores.	Simplified to one score rather than two. Changed to a five point scale rather than 11, with clear boxes to tick.

The published article from this pilot study is included in Appendix A.1.

Chapter 4: Method

Study design

This was a prospective, observational, cross-sectional point prevalence, and cohort study. The main aim of the research was to determine the prevalence of UTI in young children presenting in primary care with an acute illness.

In order to determine whether a child had a UTI or not, a urine sample was needed from all participants. In a prevalence study, the determination of UTI status needs to be independent of whether clinicians suspected UTI or not, therefore urine samples needed to be requested from all children. I therefore needed a cohort of acutely ill children recruited with systematically collected urine samples to determine the point prevalence of UTI.

I was also interested in the clinical outcomes for those found to have a UTI and wanted to compare the outcomes of children with UTI to those with borderline or negative cultures. Therefore, follow-up data collection was necessary.

Setting

Determining the prevalence of UTI among consulting acutely ill children is important to help GPs to manage these children appropriately. GPs need to know which ill children should have their urine sampled or whether UTI is prevalent enough to justify a universal sampling strategy in all children. In order to determine this, we need to know the prevalence of UTI in *that* population. For my study, it was therefore important to recruit children typical of those seen every day by primary care clinicians, which meant recruiting children from primary care as they consulted with an acute illness.

Funding

The study was awarded funding by The Welsh Office of Research and Development (WORD) with a Welsh Assembly Government /Medical Research Council Health Research Partnership Award for £139,897 with up to an additional £72,058 in service support costs (Project reference: H07-3-008; see Appendix 4.1).

Ethical approval

The study was approved by the South East Wales Research Ethics Committee Panel C (reference number: 08/WSE03/11). Several amendments were approved to extend the recruitment period and to use posters in the practices to aid recruitment (Appendix 4.2).

Other approvals

Cardiff University was sponsor for the study. The study was approved by the R&D offices of all the LHBs and Trusts involved in the study. The study was included on the UKCRN Clinical studies portfolio. The South East Wales Trials Unit (SEWTU) supported the study and provided administrative support.

Study name and logo

I wanted a study acronym and logo to help practices to remember the study. I called the study 'EURICA: The **e**pidemiology of **ur**inary tract **i**nfections in **c**hildren with **a**cute illness in primary care'. I discussed logo ideas with Jan Sharp in the Medical Illustration department at Cardiff University and she designed the first logo, which was inspired by the blocks of colour on urinary dipsticks (see Figure 4.1). When I was designing a poster for practices to aid recruitment, I felt that we needed a picture and I discussed ideas with Jan in medical illustration again. I asked if she could design a picture of a person as if it had been drawn by a child, perhaps juggling the EURICA blocks. She designed the logo 'Eddie' in Figure 4.2.

Figure 4.1: The EURICA study logo

Figure 4.2: The second EURICA study logo

I used both logos on the posters and recruitment updates and letters to practices.

Sample size calculation

I calculated that a sample size of 1100 would give a 95% confidence interval of +/- 1% around a prevalence rate of 3%.[148] In the pilot study (n=99), urine samples were obtained in 75 (75.8%) but a laboratory result was only available in 71(71.7%). Urine samples leaked or were lost in transit in 4 (5.3%). If a laboratory result is only available in 72% of recruited children, a sample size of 1528 recruited children would be needed to give a sample size of 1100 children with urine results. Therefore I aimed to recruit 1600 children. The sample size calculation was not adjusted to allow for clustering by practices and there was no calculation to determine number of practices which should be recruited.

Recruitment

Recruitment period

The WORD grant funding was from 1st April 2008 – 31st March 2010. However, due to recruitment problems, the recruitment period was extended until August 2010; with follow-up until February 2011 (approvals to extend the study time were given by WORD and the Ethics committee).

Practice selection

Several key decisions needed to be made before deciding which practices to approach to take part in the study:

1) Were urine samples going to be analysed by the local laboratory which usually analysed samples for the practice or were all urine samples going to be analysed by a central (research) laboratory?
2) How were urine samples going to be transported to the laboratory?
3) How were clinicians going to receive laboratory results and act on them?

Laboratory choice

The advantage of using local laboratories would be that the practices' normal transport could be used, and results would be returned to clinicians as usual, in a format that they were familiar with. The disadvantage would be that different laboratories may have had different procedures for analysis and reporting urine samples, which would introduce variation into the results. Using one central laboratory would reduce the chance of laboratory variation, however transport would be more difficult; practices would have to deal with a procedure

which was different from normal; and clinicians would receive results in a format which they were not familiar with and may have difficulties with interpretation.

For these reasons, I decided that we should use the local NHS laboratories for the study. Initially, the best option seemed to be to recruit practices from one area which used the same local laboratory. This strategy would keep research procedures as close to normal practice procedure as possible, but would not introduce the problems associated with using different laboratories. I decided to target practices in the Cardiff and Vale area.

Unfortunately, only nine practices in Cardiff and the Vale agreed to take part in the study. Recruitment of children was slower than expected. Therefore I had to extend recruitment into other parts of Wales, despite the potential problem of using different laboratories. Laboratories in Rhondda Cynon Taf (RCT), Rhyl and Haverfordwest agreed to take part. Once the laboratories had agreed to take part I could approach practices.

Transport of urine samples to laboratory

Having decided to use the local NHS laboratories meant that the normal surgery transport of clinical specimens could be used. In addition to reducing costs and minimising new procedures for practices which may have hindered recruitment, I felt that using routine NHS processes strengthened the study design. The estimate of UTI prevalence from my study would be based on urine sampling and analysis as it occurred in routine general practice and my study findings would be directly applicable to current every day general practice.

Urine samples were usually collected by NHS (National Health Service) transport at approximately midday. As is normal practice, the transport vehicle may have collected samples from other practices too and so transport of samples from the practice to the laboratory may have taken a few hours. There was no refrigeration of samples during transport.

Receipt of NHS laboratory results by clinicians

It was essential that the results of any urine samples were seen by the clinicians who were responsible for assessing and treating the child. I emphasised to everyone participating in the study that the clinical management of the child rested entirely with the treating clinician. The researchers would only receive a copy of the urine sample results and would not inform

participants of the result or advise on management. Using the normal microbiology forms ensured that the result would be made available to practices in the standard way (usually electronically).

After discussion with microbiologists, initially at Cardiff and Vale (Dr Howe), but subsequently with those at all the laboratories taking part, we agreed that urine samples in the study would be processed in the normal way, using standard containers and forms, with results sent to practices. A copy of the result would also be sent to me in the research office. So that laboratory scientists processing urine samples would know to do this, study samples would be labelled with a red 'EURICA' sticker.

Practice selection

Initially I targeted practices in the Cardiff and Vale area with two or more GP partners or two or more practice nurses. Although ideally a random sample of practices would be recruited, following my experience with the pilot study, I felt that the study was probably not feasible for small practices with fewer resources. Unfortunately there were not enough interested practices among this group of practices and so I subsequently invited all the practices in Cardiff and Vale to participate, and later other practices in other areas.

Practices were initially sent a letter (Appendix 4.3). This was followed up with a telephone call to the practice manager. If practices were interested I visited the practice to explain the study in more detail. Often, this initial visit was to a practice meeting, which sometimes consisted of all the doctors, nurses and administrative staff, and sometimes just one or two nurses and doctors. Not all of the practices which initially expressed an interest or who requested a visit, ultimately agreed to participate in the study.

Recruitment of practices

Two changes in the NHS had a significant impact on recruitment of practices:

1) Until April 2009, for each practice which agreed to participate in the research study, a site specific information (SSI) form had to be submitted to the Ethics committee so that they could approve the practice for the study. Although this required information from the practice and a Curriculum Vitae (CV) for the lead GP, it generally only took

approximately two weeks for the ethics committee to approve the practice for the study once they had received the paperwork.

From April 2009, a new process was initiated called "SPARC" (Streamlined NHS Permissions Approach to Research Cymru). Although this process was set up to improve both the quality and efficiency of Research and Development (R&D) approval processes, it complicated the process of obtaining approvals for subsequent practices for my study. Where SSI approvals had previously taken a couple of weeks, the process took many months. As responsibility for the SSI approvals moved from the ethics committee to the local health boards, it is difficult to determine to what extent the delays encountered were due to SPARC and to what extent they were due to the NHS restructuring which occurred in October 2009 (below).

2) In October 2009, there was a major restructuring of the NHS in Wales. Until this point there had been 22 Local Health Boards (LHBs; covering primary care) and seven Hospital Trusts (secondary care). From October 2009, these merged, with a resultant seven LHBs which covered both primary and secondary care services for each area, with three overarching NHS Trusts.

   SSI approvals had to be obtained from LHBs instead of the ethics committee from April 2009 onwards. Unfortunately, LHBs were in a state of re-organisation and uncertainty. Table 4.1 shows a summary of procedures before and after the changes of April and October 2009.

Table 4.1: R&D approval procedures before and after the changes in April and October 2009

Approvals for:	Old system: before April 2009	New system: after April 2009 but before Oct 2009	New system: Oct 2009
Practices to participate	1) Apply to primary care LHB directly to conduct research in practices in their area (1-3 months) 2) SSI approval for individual practices from the Ethics committee (1-2 weeks)	1) Apply to SPARC for each practice and primary care LHB* 2) Apply to each primary care LHB* directly	Apply to SPARC for each LHB/Trust* and for practice specific approvals
Laboratories to participate	Apply to hospital NHS trust directly (1-3 months)	1) Apply to SPARC for each hospital NHS Trust* 2) Apply to hospital NHS Trust* directly	

* The primary care LHBs and hospital NHS Trusts were replaced in October 2009 with a smaller number of LHBs covering both primary and secondary care

Approval for the first surgeries to participate in the study prior to these two changes was relatively straight forward. However, after April 2009, approval for further practices to take part in the study took 10 months. Two surgeries in Rhyl and five surgeries in Haverfordwest had agreed to participate in the study. Unfortunately, all but two of these practices withdrew their agreement to participate during this process.

CRC-Cymru

The Clinical Research Collaboration in Wales (CRC-Cymru; now NISCHR-CRC) agreed to support recruitment for my study.[165 166] CRC-Cymru was funded by the Welsh Office of Research and Development (WORD) to support research.

Research officers from CRC-Cymru helped with recruitment of practices, distribution of equipment, collection of CRFs and consent forms, occasional practice visits and in some practices, recruitment of children and data collection. There were initially two research officers involved in my study (based in Cardiff), but later representatives in West and North Wales were also involved.

Training practices

Once a practice had been approved to participate in the study, I visited the practice to train them in study procedures and to provide study documents and equipment. A research officer from CRC-Cymru would accompany me when possible.

The minimum attendance I required from practices for training was from the lead GP and the practice nurse who would be taking consent and collecting data. I described the study procedures and discussed any questions or queries. I provided a summary of processes for the study documents and urine samples (see Appendix 4.4) and a copy of the summary of the NICE guideline.[1]

I emphasised:

- The informed consent procedure.
- The broad inclusion criteria.
- The importance of obtaining urine samples on all children.
- The two methods for obtaining urine samples.
- The observational nature of the research study.
- The clinical responsibility for management of the child remaining with the GP.
- Labelling of urine samples with the red EURICA study label in addition to the child's identification label but otherwise using the normal procedures for urine samples.
- Completion of a recruitment log to include children who were approached or eligible for the study but not recruited (Appendix 4.5)

Informed consent

Parents or carers were provided with an introductory letter (Appendix 4.6) and patient information leaflet (Appendix 4.7). They were given time both to read them and ask questions, and asked to sign the consent form (Appendix 4.8) if they were happy to participate in the study. All the documents were approved by the Ethics committee.

Payments

Practice payments

Practices were reimbursed for the time taken to complete study procedures and obtain a urine sample using service support costs. They were paid £30 for every child recruited with a consent form and CRF and an additional £15 for every urine sample obtained.

Laboratory payments

Laboratories were paid £5 for every urine sample analysed using service support costs.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were clearly stated on the patient registration form (see Appendix 4.9). Children were only included if:

- They were less than five years old *and*
- They had an acute illness with a duration of 28 days or less *and*
- They had not already been included in the study (those who had participated in the pilot study were eligible for the main study) *and*
- The parent or carer provided written, informed consent.

Children were excluded if:

- They were taking regular long-term antibiotics (daily for the past 28 days or more) *or*
- They were currently having chemotherapy *or*
- They were currently taking oral prednisolone of 10mg or more daily (or equivalent) for the past 2 weeks or longer (taking inhaled steroids was not an exclusion criterion).

In the pilot study, one of the exclusion criteria was radiological evidence of urinary tract abnormalities (including antenatal scans). For the main study, I wanted to make the recruitment as straight forward as possible, and keep exclusion criteria to a minimum, so that practices would recruit the majority of children. Following discussions with my supervisors, we felt that there would be relatively small numbers of children who would have known urinary tract abnormalities and we felt that it would be informative to collect data for these children, and if there were sufficient numbers, to determine if children with antenatal urinary tract abnormalities were more at risk of UTI or not. This group of children was therefore not excluded from the main study.

I discussed the inclusion and exclusion criteria with my supervisors and we felt that children taking long-term antibiotics, oral steroids or who were currently receiving chemotherapy were likely to have a higher risk of infection and were likely to be treated differently by GPs. Therefore these children were excluded from the study. Excluding children on long-term antibiotics would also exclude children being treated for recurrent UTI. Children with diabetes, or other medical conditions or family history, or who were taking other medication were not excluded from the study, but these data were collected on the CRF.

Children were excluded if they had already participated in the study in order to keep the analysis straight forward. In some ways this was unfortunate, as children tend to consult several times a year with different illness episodes[44] and I was interested in what proportion of acute illness consultations were due to UTIs, and so ideally would have liked to have included children each time they consulted. However, this would have made the statistical analysis more complicated. The data collected from a child who has already been included in the study are not independent from the data collected from the same child during a previous episode. Therefore the data from children included more than once would need to be analysed differently. It would also mean that a larger sample size would be needed (to allow for intra-cluster correlation) for the same confidence interval, depending on how many children were included more than once.

Data collection

Case Record Form (CRF)

I designed the CRF in three sections (Appendix 4.9 - 4.11). The CRF was designed using Teleform (version 10.4.1). Teleform is a package which allows data from scanned documents to be entered directly into a database.

Section 1 was the registration form with contact details (Appendix 4.9). This was printed on white paper and a copy of this was faxed by practices via the confidential fax line to the research office along with the consent form once the child had been recruited to the study. Section 2 was printed on yellow paper and was completed by the practice or research nurses (Appendix 4.10). Section 3 was printed on orange paper and completed by the treating clinician (Appendix 4.11). Sections 2 and 3 were kept by the practice and collected once per month by CRC-Cymru research officers. The CRFs were scanned and checked using

Teleform with the help of administrative staff. Administrative staff checked that the software had scanned data in correctly and produced a record of queries and discrepancies which I then checked against the raw data. Queries and decision rules concerning data cleaning were discussed with Professor Hood. The data were then exported into SPSS for further data cleaning and analysis.

Symptoms and signs

The symptoms listed were similar to those used in the CRF for the pilot study (Appendix 3.2). Following discussions with the nurses involved in the pilot study, I merged the variables 'not playing well' with 'low energy/tired', and I merged 'clinginess' and 'needing extra care' as they felt that these variables were measuring the same symptom. I split 'constipation' into 'constipation now' and 'constipation in the past' for clarity, and I added 'sore throat' as this was a common symptom which I had missed out on the pilot study CRF. I added 'blood in the urine' and 'poor urine flow' as 'haematuria' and 'dysfunctional voiding' were listed as possible presenting symptoms of UTI in the NICE guideline.[1] I grouped symptoms into four parts on the CRF to make it easier to read.

A five point score (0-4) was used for parental and GP illness scores, rather than the 11 point score which had been used in the pilot study. This was to simplify the scoring, limit the time needed to complete the CRF and to simplify the analysis.

Background information and risk factors

I wanted to collect information on all clinical factors potentially useful for ruling UTI in or out (see Table 4.3 below). The difficulty was to balance collecting as much information as possible whilst not making the CRF too long and time consuming to complete.

Examination findings

Nurses were asked to record temperature, pulse rate and respiratory rate in section 2 of the CRF. Practices were all provided with an infra-red ear thermometer. GPs were asked to record their examination findings in section 3 of the CRF.

Tables 4.2-4.5 summarise the symptoms, examination findings, potential risk factors and management recorded on CRFs.

Table 4.2: Symptoms recorded on CRF (as 'Yes/No' variables)

Runny or blocked nose	Irritable/grouchy	Poor feeding/appetite	Bed wetting/clothes wet when previously dry
	Clinginess/needing extra care	Diarrhoea	
Sore throat		Constipation now	Smelly urine
Earache/holding ear	Low energy/tired/lost interest in playing	Constipation in the past	Dark or cloudy urine
Cough		Vomiting	Pain/crying on passing urine
Difficulty breathing	Poorer sleep	Nausea	Blood in urine
Hot/feverish	Muscle aches/pains	Abdominal pain	Poor urine flow
Rash	Poor weight gain/weight loss	Colic/grimacing	Increased urinary frequency/no. wet nappies

Table 4.3: Other background information recorded on CRF from parents

Highest temperature measured prior to GP visit
How unwell do they feel their child is (0-4)?
Has the child had paracetamol for this illness?
Has the child had ibuprofen for this illness?
Past history of UTI
Past history of asthma
Past history of diabetes
Past history of eczema
Past history of high blood pressure
Past history of kidney or bladder disease
Has the child had illnesses in the past with a high temperature but no obvious cause?
How many weeks did the pregnancy last?
Was the child breast fed?
Were any antibiotics taken during the pregnancy?
Were there any abnormalities of the child's kidneys, bladder or ureters on antenatal ultrasound?
(For boys) Has the child been circumcised?
Family history of UTI during childhood
Family history of kidney or bladder problems

Table 4.4: Examination findings recorded on CRF

Temperature	Ear examination	Rash
Pulse rate	Throat examination	Dehydration
Respiratory rate	Chest examination	Jaundice
Urine dipstick results	Abdomen examination	Spinal lesion
		Fontanelles

Table 4.5: GP impression and management

How ill do they feel child is (0-4)?	Same day hospital referral
Working diagnosis	Hospital referral but not same day
Any medication prescribed	

Once practice nurses had obtained consent and completed Sections 1 and 2 of the CRF, the child was seen by the GP who examined and treated the child according to their normal clinical practice and then completed Section 3 of the CRF.

Urine sampling

Obtaining a urine sample

Obtaining the urine sample was the most important aspect of the research study. Once consent had been obtained, but usually before the CRF was completed, nurses explained to parents how to obtain a urine sample. There were two methods of obtaining a urine sample (see section below). If a nappy pad was to be used this was inserted as soon as possible after consent, to increase the likelihood of obtaining a urine sample before the child left the practice. Potties, with sterile bowls inserted, were provided to practices to help obtain clean catch samples in older children. The aim was to obtain the urine sample whilst the child and parent were going through the process of study data collection and whilst waiting to see the GP. After the child had been seen by the GP, they could be seen again by the practice nurse to retrieve the nappy pad or clean catch urine sample.

The urine sample was tested with a urinary dipstick and recorded in Section 2 of the CRF. The sample container and microbiology form was labelled with the child's personal details as normal, but in addition a red 'EURICA' label was added to the sample container and to the microbiology form. It was then taken to the laboratory using the practices' usual transport. If the urine sample was obtained in the afternoon (after the sample collection time), practices were asked to store the urine sample in the fridge overnight as recommended by guidelines.[1]

Children were not recruited after the last sample collection on a Friday due to the long delay which would have occurred between obtaining a urine sample on Friday afternoon and transport to the laboratory on the following Monday.

Urine sampling method

NICE have recommended that the clean catch urine collection method is used as first choice, but that nappy pads are a suitable alternative if clean catch is not feasible.[1] In the pilot study, parents using both methods of urine sampling (nappy pad and clean catch) had reported that they were straightforward and easy to use. The practices were supplied with the equipment

needed for both methods. This included a sterile plastic bowl (for clean catch) and the 'Newcastle' collection pads.

The Newcastle collection pads came in a packet containing two pads and a syringe. The nurses and parents were advised to check the pads every 10 minutes to see if urine was present. If the pads were soiled, the child needed to be cleaned and a fresh pad used. The syringe was provided to extract the urine from the pad. However, when I discussed the method with the nurses following the pilot study they described this as very difficult. Instead, they had been squeezing the urine out of the nappy pad. At this time I could not find any literature suggesting that this was or was not acceptable. I discussed the matter with one of the microbiologists (Dr Howe). I was particularly concerned that fibres from the pads might interfere with the analysis but it did not appear to be a problem. Since then, the HPA Standards for Microbiology report has been published.[89] In this, they comment on the use of nappy pads and the syringe to extract the urine and state, "if difficulty is experienced in withdrawing urine, the wet fibres may be inserted into the syringe barrel and the urine squeezed directly into the container with the syringe plunger".

I also provided practices with leaflets describing how to collect the urine using each method which they could give to parents (Appendix 4.12). These were developed for a previous research study and I obtained permission from the authors to use these.[46]

Urine containers

During the pilot study I had been surprised at the number of urine samples which were reported as 'leaked in transit'. If the urine sample leaked into the bag on the way to the laboratory, it could not be analysed. In the pilot study, 4% of urine samples leaked. At the beginning of the main study, there seemed to be even higher numbers of urine samples leaking in transit. I discussed this problem with Dr Howe and he advised me that some urine sample containers (white top universal containers) were more prone to leaking than others and that the NHS had started to use cheaper containers in recent years which were more prone to leaking. He recommended a slightly more expensive white topped universal container which I provided to practices to try to reduce the problem. Some laboratories required different types of urine collection containers (e.g. red topped boric acid containers) which they provided to practices.

Laboratory results

The NHS laboratory results were sent to GPs in the normal way. GPs managed children according to their normal clinical practice. Advice for GPs, if they required it, on the management of children or interpretation of urine culture results, was available for the duration of the study from a consultant paediatric nephrologist, Dr Judith van der Voort.

A copy of the result was sent to me by laboratories using Royal Mail. Results were entered into an Access database by Mandy Iles (research administrator). I checked the accuracy of data entry for urine results in 10% of cases. Data entry was accurate for the majority of results. However, I found that there were some errors and missing information for some of those with positive or borderline results and so I double checked the data entry for all cases with positive or borderline results.

Follow-up

For any children with positive or borderline urine results, I aimed to complete a telephone follow-up interview at two weeks after the index consultation, and no more than 4 weeks following the index consultation.

I entered the data from the telephone follow-up interviews directly into the Access database. The data collected are shown in Table 4.6 and Appendix 4.13.

Table 4.6: Data collected at 2 week telephone follow-up

- Has the child completely recovered?
- How many days did the illness last?
- Has the child been admitted to hospital?
- Has the child been admitted to hospital?
- Has the child seen the GP, nurse, A+E, OOH since the initial consultation?
- Has there been any contact with NHS Direct, a pharmacist or a specialist?
- What method was used to obtain a urine sample?
- How easy (0-5: 0=difficult- 5=easy) was it to obtain a urine sample in this way?
- How many other children live in the house?
- Has anyone else in the house had illnesses or antibiotics in the past 3 months?
- Does anyone living in the house work in a hospital, nursing/residential home, GP surgery, school or other medical/child care facility?
- Does the child attend school, nursery, day care, breakfast club or have a child minder?

I made at least three attempts to contact parents at different times of the day. If the telephone number did not work or I had the wrong number I contacted practices to see if they had any other telephone numbers listed for the child or their parents.

6 month follow-up

All children from whom a urine sample had been obtained were targeted for the six month notes review follow-up. This was a single page form and practices were paid £10 for each follow-up form which they completed (Appendix 4.14). Table 4.7 shows the data which were collected on these forms.

Table 4.7: Data collected at 6 month notes follow-up

Number of GP re-consultations	Any hospital referrals
Number of acute hospital admissions	Any investigations of the urinary tract (or referrals for these)
Number of OOH/A&E contacts	Ultrasound scan
Number of courses of oral antibiotics	DMSA scan
Number of urine samples	MCUG scan

Outcome measures

Primary outcome measure

The primary outcome measure was the prevalence of UTI, defined as pure or predominant bacterial growth of $>10^5$ colony forming units (cfu)/ml of urine on NHS laboratory culture.

Secondary outcome measures

- Symptoms, examination findings and risk factors at presentation and predictive values
- GP working diagnosis and management and comparison between UTI and non-UTI groups
- Near-patient urinary dipstick results and predictive values
- Duration of illness with comparison between UTI and non-UTI groups
- Re-consultation, hospital admission rates and courses of oral antibiotics for six months after recruitment with comparison between UTI and non-UTI groups
- Hospital referral and imaging of the urinary tract for six months after recruitment with comparison between UTI and non-UTI groups.

Data cleaning

The CRF and six month follow up data from Teleform were combined with the laboratory urine results and telephone follow up data from Access. Data were checked, cleaned, anonymised and analysed using SPSS version 16.

I kept a log of data cleaning and changes which I made (Appendix 4.15) and decision rules which were agreed on with one of my supervisors (Professor Hood; Appendix 4.16).

During the data cleaning process, I checked individual variables for missing data and unusual values. I looked at the data range for continuous and date variables, searching for outlying values.

Missing information

For most questions in the CRF, where questions required a 'Yes' or 'No' response, missing information was re-categorised as 'No' for the analyses. Responses of 'not applicable' and 'don't know' were also analysed as a 'No' response. I was interested to know whether there was an association of a 'Yes' response with UTI, for each variable, compared with not having a 'Yes' response. For the same reason, abnormal examination findings by the GP were compared with those from whom abnormal findings were either not reported on the CRF or if this information was missing.

For variables such as 'highest temperature recorded by the parent/carer' or for the illness severity scores (parents and GPs), missing information remained as missing information and the analysis was only conducted on those in whom it had been completed. In the case of the GP's working diagnosis, I considered missing information as a response in its own right, as GPs may have left this response out if they were unsure of the diagnosis.

Grouping variables

I grouped children according to age, with the same age-ranges used in the NICE guidelines.[1] I used a threshold of 38^{o}C to create a binary variable for temperature as this is used by most previous studies to define fever. [45 58-62 66 68-70 72 82 99-102 129 130] For some categorical variables (for example: working diagnosis, number of courses of antibiotics at follow up), the groups were too small for statistical tests and in these cases I grouped some categories together. For

each case where I have done this, I have described which categories I have grouped together and provide justification for this in the results chapter.

I only included children who had provided a urine sample within two days of the initial recruitment (index) consultation. I calculated this based on the date of consultation and consent on the CRF and the date of the urine sample. I wanted to ensure that the urine sample result related to the presenting symptoms and signs of the acute illness at the index consultation.

Statistical analysis

I calculated the prevalence and associated confidence intervals using Wilson's method, which is a method most appropriate for small proportions as advised in Newcombe's paper.[148]

For the analysis of binary variables, I used Chi-square (χ^2) tests to look for association of variables with UTI. Where the numbers were too small to use χ^2 tests I used Fisher Exact tests. For associations between UTI and ordinal variables with more than two categories, Chi-square tests were used (not Chi-square test for trend).

For the continuous variables (pulse rate, respiratory rate and temperature) I plotted histograms to determine whether they were normally distributed. For those which were normally distributed I presented mean, standard deviation and used the t-test to compare groups. For those which were not normally distributed I calculated median, inter-quartile range and used the Mann-Whitney U test to compare groups.

Throughout my thesis, I have presented p-values to two decimal places and all other figures to one decimal place.

Multilevel modelling

I explored the impact of my two level sampling (practices and patients) using the intra-class coefficient (ICC). This estimated the proportion of variability in the prevalence which was attributable to the sampling of practices rather than variation due to sampling of children within practices. This is explained further in the results chapter. The two-level sampling

appeared to result in only a small amount of clustering. Therefore, I used single level multivariable analysis techniques.

Multivariable analysis

I used logistic regression to determine which presenting symptoms and signs were most associated with UTI. I used the univariable analyses as a screening tool to determine which variables to enter into my logistic regression analysis. Symptoms and signs with a p-value of <0.1 on univariable analysis were entered into a forward stepwise logistic regression using SPSS. Where there was significant association between individual symptoms using chi-square tests (e.g. dysuria and urinary frequency), I entered these variables in combination as well as individually into the model. I assessed the model fit using the model χ^2 and Nagelkerke R^2 statistics.

I calculated the probability of UTI for all combinations of the variables in the model using the equation for the logistic regression:

$$p(Y) = 1/1 + e^{-(-b0+biX1i+b2X2i+\ldots+bnXni)}$$

Where p(Y) is the probability of Y occurring (in this case UTI); e is the base of natural logarithms, and b_n is the regression coefficient of the corresponding variable X_n.[167]

I used these probabilities and their associated confidence intervals to propose a urine sampling strategy for GPs. I compared urine sampling using my proposed sampling strategy with sampling based on GP suspicion and sampling based on NICE guidelines.

If any of the features listed in the table of presenting symptoms and signs in the NICE guideline (see Results chapter, Figure 5.9)[1] were present for that child, I assumed that a urine sample should have been taken in that child, unless there was evidence of an alternative site of infection. I determined whether there was evidence of an alternative site of infection from the GP working diagnosis. If the working diagnosis was listed as upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), tonsillitis, gastroenteritis, conjunctivitis or otitis, I considered there to be an alternative site of infection present.

GPs were deemed to have suspected UTI if UTI was mentioned at all in the working diagnosis question of the CRF.

Sources of bias

During the design of the study, I was aware of the importance of minimising the chance of bias, particularly selection bias. The main problem with many of the published studies concerning UTI in children was the inclusion of children only if the child had been suspected of having UTI by the clinician. The study population would therefore be different from the target population, biased towards children who were suspected of having UTI by the clinician. This may have resulted in biased associations with presenting symptoms and signs. I tried to minimise the risk of this happening in my study by asking surgeries to recruit (all) sequentially ill children and obtain urine samples on all of them, irrespective of their presenting symptoms and signs or level of UTI suspicion. I also arranged for reimbursement for surgeries to be split so that some of the money would not be reimbursed unless a urine sample was obtained. This was in part to reflect the added time and effort required to obtain a urine sample but also to encourage urine sampling on all children and to hopefully minimise selection bias by GPs and nurses.

I was aware that seriously ill children who were admitted acutely to hospital were less likely to be recruited, as neither clinicians nor parents would want to delay admission to hospital because of study procedures. I tried to address this by encouraging practices to request consent for the study but no other study procedures, if possible prior to admission. My main outcome measure was UTI prevalence and the CRF only addressed secondary study objectives. A urine sample would most likely be obtained at the hospital and I could find out the culture result through the hospital if I had consent for the study and follow-up procedures.

I also considered attrition bias in my study design. This was potentially relevant for the clinical outcomes measured during follow-up, particularly for the telephone follow-up. I asked nurses to check telephone numbers at recruitment. Section 1 of the CRF recorded this data. I attempted to contact parents at least three times on different days and different times to try to avoid losing them from follow up.

Ethical considerations

The main ethical issues affecting my study were informed consent and confidentiality of data. Both these aspects of my study were assessed, discussed at the meeting, and approved by the Ethics Committee. The Access database which had identifiable data on it was password protected, and only accessed by two members of the study team (Amanda Iles (Research Administrator) and me). All data were anonymised before transfer to SPSS for analysis. The paper CRFs and consent forms were stored in locked filing cabinets in the South East Wales Trials Unit (SEWTU).

There was also the potential risk that if more children were identified as having UTI than would happen in normal clinical practice, and if some of these results were false positives, those children may receive unnecessary antibiotics or unnecessary investigations. I discussed this issue with my supervisors and with the ethics committee. According to current guidelines, an ill child found to have a positive urine culture would be considered to have a UTI and treatment and follow up investigations would be advised. However, we agreed that the responsibility for the clinical management of the child would be entirely up to the treating clinician. In recognition of this potential difficulty for clinicians, we approached a consultant paediatric nephrologist (Dr Judith van der Voort) who agreed to be available to provide advice for clinicians for the duration of the study.

I used the STROBE guidelines and checklist to inform my approach for reporting my findings (Appendix 4.17).[168]

Representativeness of sample

I have sought a sample of children which is representative of the larger population of children presenting in UK general practice with an acute illness. I will be drawing conclusions about all acutely ill children aged less than five years presenting to the GP in the UK with an acute illness (target population) based on my findings in the sample of children which was included in this study (sample). It is therefore important to be confident that the sample is representative of the sampled population, or if not, to be able to describe and understand any bias; and that the sampled population is representative of the target population.

In this chapter I have described how, during the design of the study and development of the study protocol, I tried to ensure the resultant sample would be representative of the target population and minimise selection bias.

In the Results chapter, I will describe the sample and compare it to the sampled population and I will also describe the sampled population and compare this to the target population. I will consider to what extent selection bias may have occurred and what impact the multi-level sampling method may have had.

In the Discussion, I will consider to what extent my results can be generalised to the target population.

Chapter 5: Results

In this chapter I will present results for the main and secondary outcomes (the prevalence of UTI; the sensitivity and predictive values of clinical features and point of care dipsticks in predicting UTI; and the clinical outcomes for children with UTI). I will also describe the development of a clinical decision aid for GPs. However, before I present these findings, I will consider the representativeness of my study sample (practices and children).

Sample

Description of sample

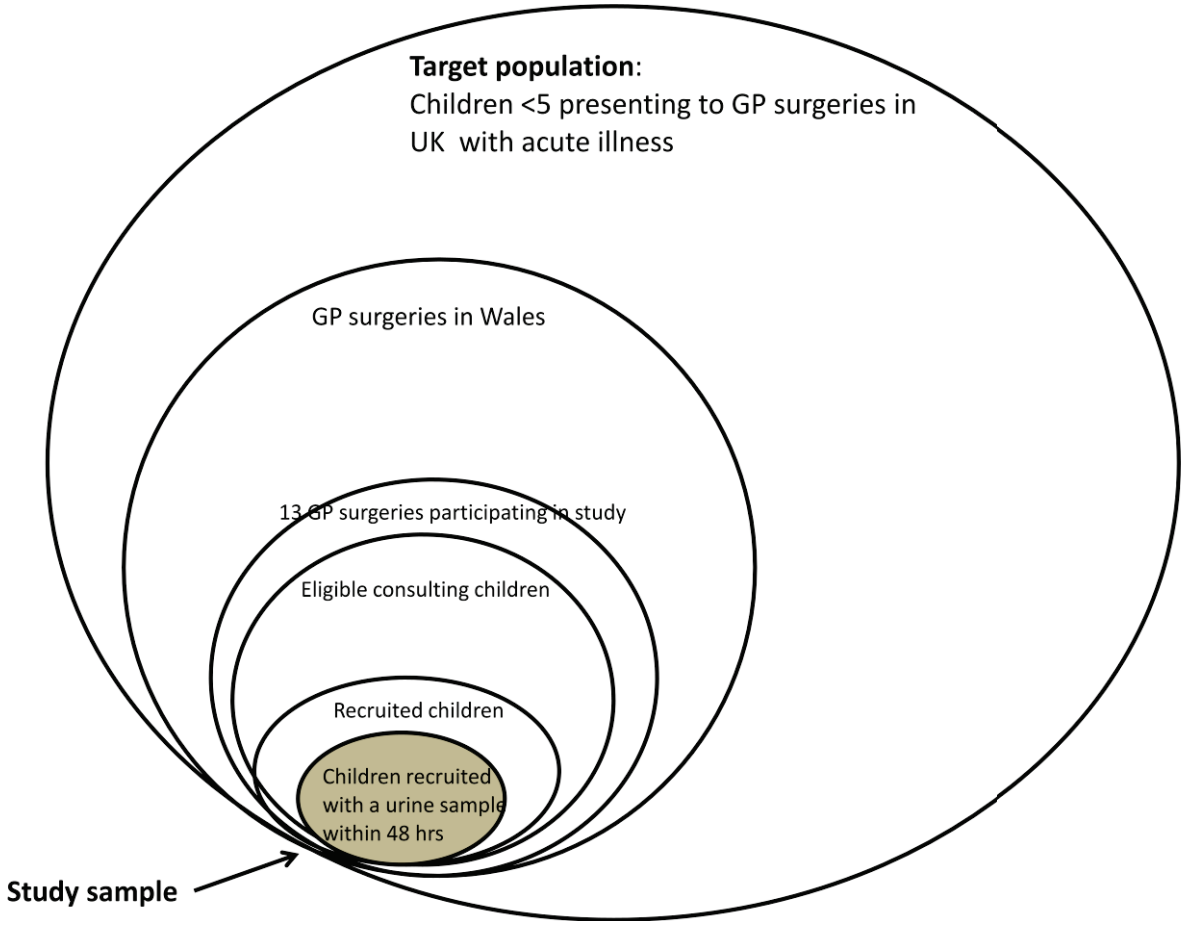
I obtained a sample of children in a two stage sampling procedure:

1) Sample of GP practices.
2) Sample of acutely ill children from practices.

In order to determine how representative my sample is of the target population (acutely ill children <5 years old in UK general practice; Figure 5.1), I have considered how similar my sample of GP practices are to UK GP practices in general; I have described the proportion of potentially eligible children recruited by practices; and I have then considered my final sample and compared it with those who were potentially eligible but either not recruited or recruited but not able to provide a urine sample within 2 days. Figure 5.1 shows a representation (not to scale) of my sample and the target population. I have also explored the variation in the main outcome (prevalence) across practices and laboratory areas to see if these are significant variables to consider when generalising my findings.

Headline: 1003 children were recruited from 13 General Practices. Urine samples were obtained from 597 children within 2 days. Participating practices had larger list sizes than the average for Wales (9774vs. 6242) and had a slightly higher proportion of registered children aged less than five years old (7.1% vs. 5.5%). Recruited children who provided a urine sample within 2 days were older than non-recruited children and those not providing a urine sample within 2 days (2.3 years vs. 1.6 years and 1.6 years). There was no significant difference in UTI prevalence by laboratory area and only 5.6% of the prevalence variance was explained by 'between practice' variation.

Figure 5.1: Representation of study sample and target population



A sample of 13 practices in Wales was recruited to take part in the study. In 2008, there were 499 GP practices in Wales and 10102 in the UK as a whole.[169] My sample of GP practices represents 2.6% of the total number of Welsh practices and 0.1% of all UK practices. Figure 5.2 is a summary box describing my study sample.

Figure 5.2: Description of sample

Target population: children aged <5 years old presenting with an acute illness (<28 days) in primary care in the UK

Sampled population: children aged <5 years old presenting with an acute illness (<28 days) from 13 general practices in Wales

Recruited children: 1003 children aged <5 years old presenting with an acute illness (<28 days) recruited from 13 general practices in Wales

Study sample: 597 children aged <5 years old presenting with an acute illness (<28 days) who provided a urine sample within 48 hours recruited from 13 general practices in Wales

1003 eligible children recruited by practices

→ 294 did not provide a urine sample

709 provided urine samples (70.1%)

→ 23 urine samples leaked in transit

→ 89 urine samples received >2 days after consultation

597 urine samples analysed within 2 days of consultation (84.2% samples; 59.5% of recruited children)

Practices

Thirteen practices participated in the study, with four associated NHS microbiology laboratories. Most practices were in South East Wales, with two practices in the West and one in the North of Wales. Practices were represented in both affluent and less affluent areas. The National Statistics Area Classification was used to describe surgery areas (Table 5.1).

The Townsend score was used as a measure of deprivation. It was calculated based on the postcode for practices. The postcodes were used to determine the ward/LSOA (Lower Super

Output Area) and the Townsend score relating to this ward was found on the Public Health Wales website.[170 171]

Table 5.1 shows the National Statistics Area Classification and Townsend scores. The practice name, post code, practice code and ward details have been removed for confidentiality. All the practices were given a centre ID number (CID) for the study.

Table 5.1: National Statistics Area Classification and Townsend score

CID	National Statistics Area Classification	Townsend score for England and Wales	Townsend score quintiles (1=least deprived
9	Urban commuter	-3.41	1
7	Well off mature households	-2.69	2
8	Well off mature households	-2.67	2
6	Affluent urban community	-2.33	2
10	Mature urban households	-0.16	3
19	Small town community	0.05	3
3	Urban terracing	0.64	4
2	Urban terracing	0.92	4
5	Small town communities	1.84	4
15	Urban terracing	3.03	4
1	Struggling urban families	4.08	5
4	Mature city professionals	4.95	5
18	Resorts and retirements	7.09	5

The table shows that the 13 practices represented a range of areas covering all quintiles with Townsend scores ranging from -3.41 (least deprived) to 7.09 (most deprived). The full range for Townsend scores is -12 (least deprived) to +12 (most deprived). Seven of the practices in my study are in the most deprived two quintiles, with four practices in the least deprived two quintiles, suggesting a range of deprivation levels was covered.

Looking at the National Statistics Area Classification, rural areas are under-represented. Most of the practices in the study were in urban or city areas.

Practice list size

Twelve of the thirteen practices provided the number of registered patients and proportion of those aged less than five years old. Table 5.2 shows this information.

Table 5.2: Practice list information

Practice (CID)	No. patients registered with practice	No. of children <5 registered with the practice	Proportion of children on practice list
1	12828	980	7.6%
2	11497	923	8.0%
3	12231	793	6.5%
4	8027	506	6.3%
5	-	-	-
6	4982	246	4.9%
7	8050	547	6.8%
8	4548	448	9.9%
9	6855	401	5.8%
10	2121	309	14.6%
15	25251	1744	6.9%
18	16084	1100	6.8%
19	11757	922	7.8%
Total	124231	8919	Mean=7.2%

The smallest practice which gave their list size was CID 10, a single-handed practice with a list size of 2121. CID 5 did not give their list size and this was the only other single-handed practice in the study. The largest list size was 25251 (CID 15).

The median list size of practices was 9773.5. This is higher than the average for Wales, which was found to be 6242 in a report in 2008.[172]

This indicates that the practices included in this study are different in this respect to practices in general in the UK. However, the two largest practices (CIDs 15 and 18) recruited only small numbers of children, representing less than 5% of all recruited children. Without including these two practices, the mean list size is 8038.5, which is still larger than the average for Wales.[172]

The larger list sizes for practices may reflect my initial targeting of larger studies; or may be due to larger practices being more likely to agree to participate, perhaps due to having more resources, flexibility or organisational structure which would make it easier to take part in research. This study required significant time to be allocated to recruiting children and

obtaining urine samples and smaller practices may not have had nurse time or room to be able to do this.

Children registered with practices

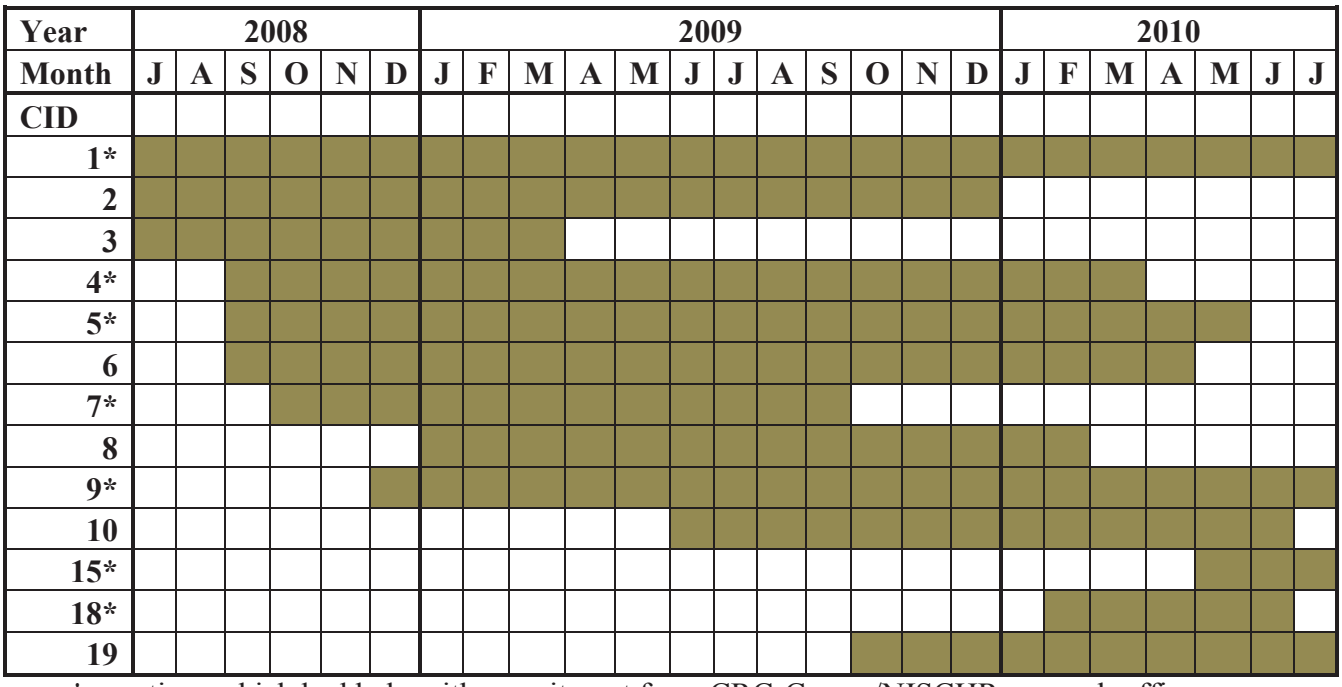
The proportion of registered patients who were less than five years old varied from 4.9-14.6% with an overall mean of 7.1%.

This is a slightly higher proportion of registered children less than 5 years old than the national average for Wales (5.5%) or England (6.0%).[172]

Recruitment rate of practices

Practices started recruitment for the study at different times (figure 5.3). Following the pilot study,[150] I felt that the best approach for optimising recruitment and keeping a high urine retrieval rate was to have a small number of practices who were very familiar with the study and intensively recruiting. It became clear that I would not reach the numbers needed from the sample size calculation in the time available if I did not recruit more practices.

Figure 5.3: Recruitment periods of surgeries

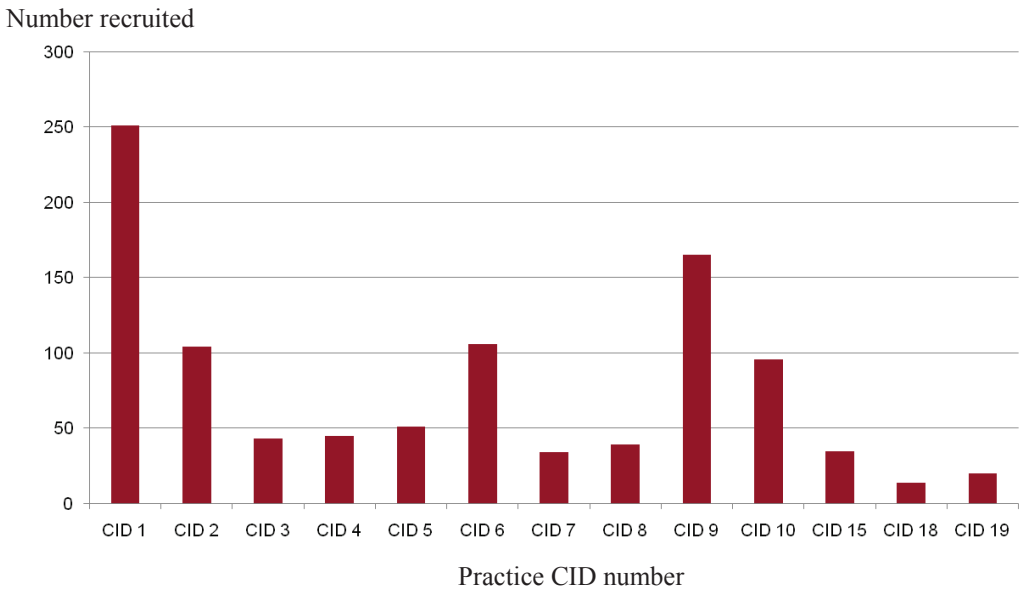


* practices which had help with recruitment from CRC-Cymru/NISCHR research officers

Unfortunately several problems affected recruitment and approval of practices to take part in the study. There was a change in the NHS structure in Wales; with the formation of seven new LHBs combining the previous primary care LHBs with the secondary care Trusts, and three overarching NHS Trusts. There was also a change in the R+D approval process and structure in Wales with the formation of 'SPARC' (see Methods, Table 4.1). This resulted in long delays in getting practices which had agreed to participate in the study approved to start recruitment. This resulted in some practices dropping out completely and several practices only had a short time to recruit (CID 15 and 18).

Some practices had help with recruitment from CRC-Cymru/NISCHR-CRC research officers. These are shown with an asterisk on Table 5.3. Recruitment varied between practices. Figure 5.4 shows the total number of children recruited per practice and figures are given in Table 5.3.

Figure 5.4: Bar chart showing numbers recruited by practice



One practice (CID 1) recruited 25% of all children in the study. CID 6 and 9 recruited 27% between them and the remaining 48% children were recruited by the other 10 practices. There was a wide variation in the time practices gave to recruitment, so recruitment rate was calculated per month. This is shown in Table 5.3. Recruitment rate varied between practices from 1.5 per month to 11.7 per month, with an overall average (mean) of 5.6 per month. The proportion of children recruited with urine samples within 2 days varied from 41%- 86% by practice (see Table 5.3) with a mean of 60%. The rate of children recruited with a urine

sample within 2 days (eligible urine retrieval rate) ranged from 1.1-6.0 per month. The two practices with the highest recruitment rates per month (CID 1 and CID 15) had below average eligible urine retrieval rates of 57% and 51% respectively. The practice with the lowest eligible urine retrieval rate was CID 5 with a rate of 41%. This was a single handed, research-naive practice in a deprived city area. They also had a reasonably low total recruitment (51) and recruitment rate per month (2.8), despite support from CRC-Cymru/NISCHR research officers.

The low urine retrieval rates in some practices may indicate that practices were only requesting urine samples from some children, perhaps in those whom they most suspected UTI, which could result in selection bias. If this was the case, there should be a difference in UTI prevalence according to urine retrieval rate with low urine retrieval rates associated with high UTI prevalence. However, UTI prevalence was not higher in the practice with the lowest urine retrieval rate (CID 5: UTI prevalence 4.8%). In the four practices with the next lowest urine retrieval rates (of less than 55%), the prevalences were 9.5%, 0.0%, 20.0% and 3.4%. The two practices with the highest urine retrieval rate had prevalences of 3.4% and 16.7%. Although the numbers with UTI are small, there does not seem to be any association between prevalence and urine retrieval rate.

Two practices had eligible urine retrieval rates of more than 80% (CIDs 7 and 18). These practices had low total recruitments of 34 (CID 7) and 35 (CID 18). CID 7 also had the lowest monthly recruitment rate of 1.5. CID 18 had a monthly recruitment rate of 3.5.

Consultation rate of children

Seven practices were able to provide the number of consultations in a year with children under 5. This is shown in Table 5.4.

Table 5.3: Recruitment numbers and Townsend score by practice

Practice (CID)	Total no. recruited (% of total)	Townsend score Quintile (1 is least deprived)	No. months of recruitment	Recruitment rate per month	No. recruited with urine samples received within 48 hrs	Rate recruited per month with urine samples within 48 hrs
1	251 (25.0%)	5	24	10.5	143 (57.0%)	5.6
2	104 (10.4%)	4	17	6.1	60 (57.7%)	3.5
3	43 (4.3%)	4	8	5.4	25 (58.1%)	3.1
4	45 (4.5%)	5	18	2.5	35 (77.8%)	1.9
5	51 (5.1%)	4	20	2.6	21 (41.2%)	1.1
6	106 (10.6%)	2	19	5.6	80 (75.5%)	4.2
7	34 (3.4%)	2	23	1.5	29 (85.3%)	1.3
8	39 (3.9%)	2	13	3.0	21 (53.8%)	1.6
9	165 (16.5%)	1	19	8.7	87 (52.7%)	4.6
10	96 (9.6%)	3	12	8.0	56 (58.3%)	4.7
15	35 (3.5%)	4	3	11.7	18 (51.4%)	6.0
18	14 (1.4%)	5	4	3.5	12 (85.7%)	3.0
19	20 (2.0%)	3	9	2.2	10 (50.0%)	1.1
Total	**1003**		**189**	**5.6**	**597 (60.0%)**	

Table 5.4: Practice list size, consultations with children and recruitment to study for seven practices

CID	No. of children <5 registered	No. of children recruited	Estimated proportion of children on list recruited	Number of face to face consultations with children <5 per year	Number of consultations per registered child per year	Recruitment rate per year
1	980	251	25.6%	5480	5.6	126
3	793	43	5.4%	4193	5.3	65
6	246	106	43.1%	2733	11.1	67
7	547	34	6.2%	1830	3.3	18
9	401	165	41.1%	1750	4.4	104
10	309	96	31.1%	2847	9.2	96
18	1100	14	1.3%	4315	3.9	42
Total	**4376**	**709**	**16.2%**	**23148**	**5.3**	**518**

CID 6 and CID 10 have high consultation rates for children and CID 7 had low consultation rates. Overall for the practices which provided this information the average was 5.7 consultations per registered child per year which is similar to published rates.[38 173]

Patients

A total of 1031 children were recruited. Twenty eight were subsequently excluded because a signed consent form was not received or because they did not fit the eligibility criteria, leaving 1003 eligible recruited children.

The recruited children in the study represented only a small proportion of all the possible consultations with children less than five years old. This is to be expected as practices were not recruiting during every surgery, in fact many allocated only one or two sessions per week to recruit for the study; not all the nurses and GPs from the surgery were involved in recruitment; some practices only recruited when CRC-Cymru/NISCHR research officers were present; and many of the consultations would represent re-consultations with children already recruited into the study (as children consult on average 5-6 times per year) and some consultations would not have been for acute illness, and would therefore not have been eligible.

Practices were asked to recruit sequentially attending children (every eligible child) *during the times of recruitment*. The main objective of this method was to limit selection bias by practices.

Recruitment logs

Practices were asked to keep a recruitment log. This is notoriously difficult in general practice research, given all the other priorities and pressures in practice. Four practices did not complete the recruitment logs. The nine practices which did complete recruitment logs listed 122 children who were potentially eligible but not recruited for various reasons. Fifty nine (48.4%) of those listed did not meet eligibility criteria.

There were 63 children listed who were eligible and were approached, but who were not recruited for various reasons. Table 5.5 shows the proportion of eligible children who were recruited as listed on recruitment logs from the nine practices which completed them. Table 5.6 shows the reasons for non-recruitment.

Table 5.5: Proportion of eligible children recruited as listed on recruitment logs

Practice (CID number)	Number of potentially eligible children approached and not recruited	Total number recruited by practice	Percentage of potentially eligible children who were recruited
1	21	251	92.3%
2	1	104	99.0%
4	2	45	95.7%
5	4	51	92.7%
6	2	106	98.1%
7	2	34	94.4%
8	17	39	69.6%
9	8	165	95.4%
15	6	35	85.4%
Total	63	830	92.9%

One practice (CID 8) had a higher proportion of potentially eligible children who were listed on its recruitment log but not recruited (30.4%). All other practices had a low reported proportion of children not being recruited if they were eligible. The most common reason cited on the logs for non-recruitment was 'not willing' or 'declined' (27.0%), and in 17.5% no reason was given. In 11.1% of cases it was stated that the parent specifically did not want to provide a urine sample or did not think their child had a UTI. Lack of time was only given as the reason in 6.3% of cases (Table 5.6).

Table 5.6: Reasons for non-recruitment

Reason for non-recruitment	Number (%)
Temporary resident/lives out of area	3 (4.8%)
Too ill	3 (4.8%)
Not English speaker	5 (7.9%)
Not enough time	4 (6.3%)
Parent did not think it was a UTI or did not want to provide a urine sample	7 (11.1%)
Person bringing child to surgery was not parent so could not give consent	6 (9.5%)
Not willing/declined	17 (27.0%)
No reason given	11 (17.5%)
Other	7 (11.1%)
Total	63

In 4.8% the reason for non-recruitment was that the child was too ill. This is important as we might expect there to be a higher prevalence of UTI among more seriously ill children and if a high proportion of non-recruitment had been found for this reason, it may indicate that the

sample was biased towards less ill children and may have resulted in a prevalence value lower than the true target population prevalence.

The low overall numbers recorded on the recruitment logs suggest that it is unlikely that they represent all the potentially eligible children presenting to the surgery. It is more likely that they represent children who were approached to take part in the study but who ultimately were not recruited. Many surgeries only attempted to recruit children on certain days or during certain clinics and recruitment logs would not have been completed for all children attending the surgery on other non-study days. Of the 63 children not recruited as indicated by recruitment logs, 34 (54.0%) were male. The median age was 1.6 years (IQR 1.0 – 3.1).

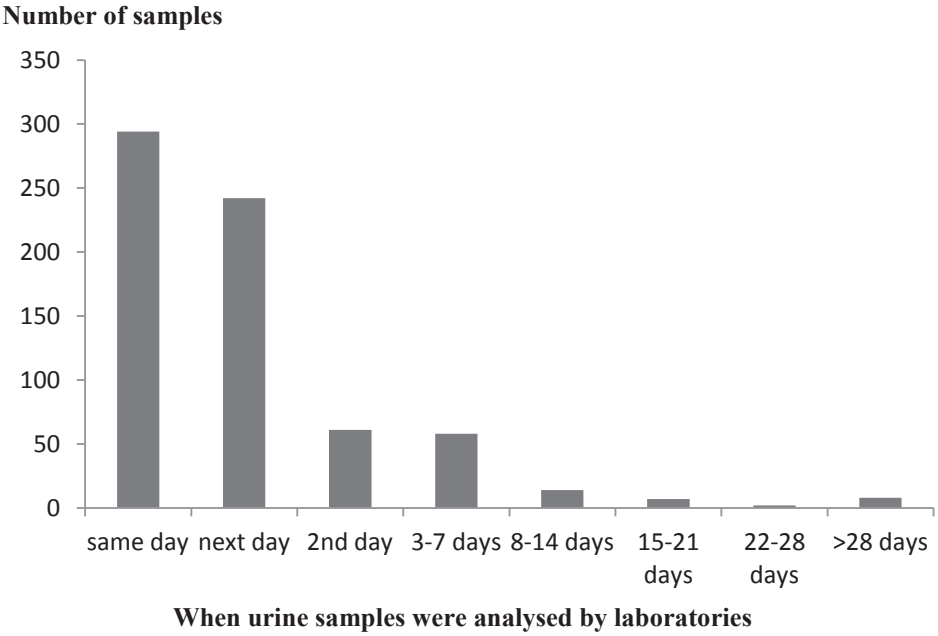
Age and gender

1003 children were included in the study. 504 (50.2%) were male and 499 were female. The median age was 1.9 years (IQR 0.9-3.3) with the youngest only 13 days old and the oldest recruited two days before his 5th birthday.

Urine samples

Urine samples were obtained from 709 (70.7%) children. There was no laboratory analysis in 23 of these (3.2%). The sample leaked in 22 and there was an accident in the laboratory in one case. Nearly half of all urine samples (49.2%) were received on the same day as recruitment. Eight samples were received more than 28 days following the index consultation and recruitment. Due to the importance of the urine sample result relating to the presenting symptoms, only those urine samples received within 2 days (same day, next day or day 2) of recruitment were used in the main analyses (n=597). Figure 5.5 shows when urine samples were received following the index consultation.

Figure 5.5: Bar chart showing when urine samples were analysed by laboratories following index consultation



Of the 597 received within 2 days, 318 (53%) urine samples were obtained before the child left the surgery. Only 294 samples were received by the laboratory on the same day, so 24 samples were presumably collected in the afternoon and stored overnight and sent the next day to the laboratory. It was much less likely that the urine sample was received within 48 hours of the consultation if the sample was not obtained before the child had left the surgery ($p<0.01$).

Urine sample collection method

The CRF recorded which of the two collection methods was used or given to parents to collect urine samples in 431 (72.2%) recruited children. This information was missing in 166 (27.8%). Nappy pads were used in all children less than 3 months old, and the majority of children less than 3 years old (74.3% aged $\geq$3 months-3 years). The clean catch method was used in all children 3 years and older. Table 5.7 shows the urine sample method by age and gender.

Table 5.7: Urine sample collection method by age and gender

Age range	Gender	Urine sampling method	
		Clean catch	Nappy pad
<3 months	Male	0	13
	Female	0	10
	Total	0	23
≥3 months to <3 years	Male	25	95
	Female	36	81
	Total	61	176
≥3 years	Male	102	0
	Female	69	0
	Total	171	0
Total		232 (53.8%)	199 (46.2%)

Final sample for full analysis

Of the 597 included in the full analysis, 313 were male (52.4%) and 284 (47.6%) female. The median age was 2.3 years (IQR 1.0-3.5). Most were aged between 3 months and 3 years old (n=349; 58.5%) with thirty-two (5.4%) less than 3 months old and 216 (36.2%) aged 3 years or older. These characteristics and some of the most common presenting symptoms are compared between those included in the full analysis and those who were recruited but not included in the full analysis. See Table 5.8.

Those not included in the full analysis were younger than those who were included. They were on average eight months younger (median age 1.6 years compared with 2.3 years; p-value <0.01). This may have been due to difficulties obtaining a urine sample in younger children. It may indicate that my sample under-represents younger children which may have affected the prevalence.

Table 5.8: Characteristics of children included in the full analysis compared with those not included.

Characteristic		Those included in full analysis (n=597)	Those not included in full analysis (n=406)	p-value (χ^2)
Age	Median age	2.3 (IQR 1.0-3.5)	1.6 (IQR 0.8-3.3)	<0.01
	<3 months	32 (5.4%)	28 (6.9%)	
	3 months – 3years	349 (58.5%)	289 (71.2%)	
	≥3 years	216 (36.2%)	89 (21.9%)	
Gender	Male	313 (52.4%)	191 (47.0%)	0.94
	Female	284 (47.6%)	215 (53.0%)	
GP working diagnosis	URTI	177 (29.6%)	121 (29.8%)	0.35
	Viral illness	90 (15.1%)	55 (13.5%)	
	LRTI	48 (8.0%)	43 (10.6%)	
	UTI	41 (6.9%)	13 (3.2%)	
	Tonsillitis	32 (5.4%)	26 (6.4%)	
	Otitis	32 (5.4%)	19 (4.7%)	
	Gastroenteritis	26 (4.4%)	18 (4.4%)	
	Other	100 (16.8%)	67 (16.5%)	
	No diagnosis	36 (6.0%)	32 (7.9%)	
GP suspected UTI		41 (6.9%)	13 (3.2%)	0.01

There was no statistical difference in gender (p=0.94) between the two groups. There was no statistical difference between GP working diagnosis when all categories were compared (p=0.35). However, when I created a new binary variable based on GP working diagnosis of UTI or not, I found that there was a statistically significant difference between those who were included in the full analysis and those who were not (p=0.01), with GPs listing UTI as a working diagnosis twice as often in those who were ultimately included in the full analysis compared with those who were not. This could indicate selection bias. However, selection bias in this case would not be because GPs were more likely to *recruit* children who they suspected may have UTI as this comparison is with those ultimately included in the full analysis with those who were not, *among all those already recruited* (n=1003) by GPs. It may indicate that GPs may have been more likely to emphasise the need for urine samples in this group of children.

For the remainder of this chapter I will be focusing only on those included in the full analysis (n=597).

Primary outcome:
Prevalence of UTI

The main outcome was the prevalence of UTI defined as a positive urine culture at the local NHS laboratory with a growth of more than 100,000 cfu/ml of a single or predominant organism. The prevalence in the sample was 35/597 (5.9%).

As discussed previously, this is the prevalence in the recruited sample who submitted urine samples within two days. To use this value to conclude what the actual prevalence is in the target population (population proportion), requires the calculation of confidence intervals (CI) (Appendix 5.1). This standard method gives 95% CI for the prevalence of 4.3-7.7%. However, this standard method is less accurate when used for proportions close to zero. For small proportions the lower confidence interval may cross zero, which is not possible. Wilson's method advised by Newcombe adjusts for this.[148] This gives the 95% CI for the prevalence to be between 4.3%-8.0%.

Variation in prevalence and potential bias

Prevalence by practice, by lab area, by Townsend score, multi-level analysis/modelling

To determine further how representative my sample population is likely to be of the target population, I wanted to examine how much of the variability in prevalence could be explained by the practice, laboratory area or by deprivation and how much variation was introduced by the two-level sampling.

There was no statistically significant variation in prevalence of UTI by deprivation of practice area (using Townsend score quintile; p=0.12).

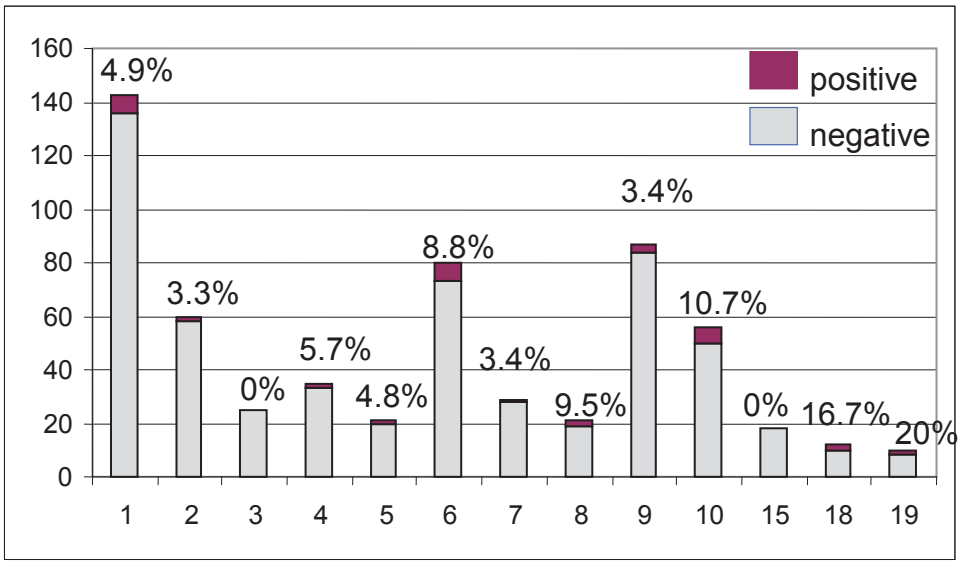
I wanted to see if the variation in prevalence was purely due to chance from sampling children or whether the prevalence was likely to vary from practice to practice. Prevalence within individual practices varied from 0-20.0% (see Table 5.9 and Figure 5.6). The practices with the lowest prevalence (CIDs 3 and 15), recruited only 25 and 18 children respectively. With a prevalence of 5.9% you would expect 1.5 cases of UTI out of 25 and 1.1 cases out of 18. Those practices with the highest prevalence (CID 18 and 19) recruited even smaller numbers increasing overall the likelihood of wide variation due to chance. In each case, there were only two cases of UTI but due to the overall small numbers a large

percentage is produced. In the case of CID 19, where two UTIs were found out of 10 recruited eligible children, the prevalence of 20% would be reduced to 10% if only one of those had not been positive.

Table 5.9: Prevalence of UTI by practice

Practice (CID)	Townsend score quintile	No. with UTI	Total number eligible children recruited by practice	% with UTI
1	5	7	143	4.9
2	4	2	60	3.3
3	4	0	25	0.0
4	5	2	35	5.7
5	4	1	21	4.8
6	2	7	80	8.8
7	2	1	29	3.4
8	2	2	21	9.5
9	1	3	87	3.4
10	3	6	56	10.7
15	4	0	18	0.0
18	5	2	12	16.7
19	3	2	10	20.0
Total		**35**	**597**	**5.9**

Figure 5.6: Bar chart showing recruitment and prevalence of UTI by practice



I wanted to see if the variation in prevalence could be explained by differences in practices. For example, were different practices recruiting children differently which could have resulted in varying prevalences or was there a difference in prevalence of UTI in the different practices due to socioeconomic or other differences, or whether it more likely simply to be sampling variation.

I was also interested in whether the variation could be due to different laboratory practices. Table 5.10 shows the prevalence with associated confidence intervals by laboratory area. There were insufficient numbers to statistically test the difference in prevalence between practices or laboratory areas. However, looking at the confidence intervals, they are all wide and all overlap, suggesting that there would be no statistically significant difference.

Table 5.10: Variation in prevalence by laboratory

Lab area	Total no. received by lab	No. not cultured due to negative microscopy	Prevalence of UTI	95% confidence intervals for prevalence
1	501	26 (5.2%)	25 (5.0%)	3.4-7.3%
2 *	18	12 (66.7%)	0 (0.0%)	0-17.6%
3	66	2 (3.0%)	8 (12.1%)	6.3-22.1%
4	12	0 (0.0%)	2 (16.7%)	4.7-44.8%
Total	597	40 (6.7%)	35 (5.9%)	4.3-8.0%

* Lab. which had SOP to only culture microscopy positive urine

One laboratory (Lab area 2) had a SOP which clearly stated that microscopy which was negative would not be cultured. All other laboratories stated that urine would be cultured if microscopy was negative. However, Lab area 1 began to use an automated microscopy machine (flow cytometer) part of the way through the study and if no bacteria were found on flow cytometry, the urine was not cultured. Lab area 3 did not culture the urine on two occasions.

Multilevel modelling

I then considered an alternative approach to see what the effect of the two levels of sampling (practices then children) may have had and to what extent practice explained the variability in prevalence rates rather than the variation expected simply from sampling children (independent of practice).

I calculated the intraclass coefficient (ICC). This represents the proportion of the total variability in the outcome that is attributable to the surgeries. It is a gauge of whether a contextual variable has an effect on the outcome. I considered the 13 practices as clusters. The ICC was calculated and adjusted to allow for different sizes of clusters.[174] All my calculations are included in Appendix 5.1.

This gave an ICC of 0.056. The ICC can be used as a measure of the degree of similarity of individuals within clusters and between clusters. The ICC represents the proportion of the total variance that is due to variation *between* clusters.

If the surgery has a large effect on the children within it, then the variability within the surgery will be small (children will behave similarly). Variability in the prevalence within surgeries is then minimized and variability in prevalence between surgeries is maximised, therefore ICC is large. Conversely if the surgery has little effect on the children then the outcome will vary a lot within surgeries, which will make differences between surgeries relatively small. Therefore, the ICC will be small.

The ICC is a ratio of the between cluster variance to the total variance and has a value which can range from 0 to 1 with 1 indicating that all the variance is explained by the between cluster variance to 0 where none of the variance is explained by the between cluster variance. **So an ICC of 0.056 means that (only) 5.6% of the total variance is explained by the between surgery variance.**

Considering whether antibiotic prescription prior to urine sampling could have affected prevalence

It is possible that a false negative culture negative result could have occurred if children were prescribed antibiotics at the index consultation and took them prior to providing a urine sample. I do not know if this could have occurred. Children who provided urine samples before leaving the surgery would not have had the opportunity to take any antibiotics. Antibiotics were prescribed in 31% (99/318) of children who provided urine samples prior to leaving the surgery and in 25% (70/279) of those who did not. Among those who did not provide urine samples prior to leaving the surgery, there was no difference in UTI prevalence between those who were prescribed antibiotics during the consultation and those who were not (p=0.33). This suggests that antibiotics were unlikely to have had a significant effect on

UTI prevalence in my study. Perhaps GPs and nurses encouraged parents to obtain a urine sample before the child started the antibiotics.

Main Findings

Primary Outcome

Headline: The prevalence of UTI was 5.9%. A further 2.8% had a borderline result. The prevalence of UTI was higher in younger children. In older children (>3 years) the prevalence of UTI was higher in girls than boys. There was no significant difference in the prevalence of UTI according to urine collection method. There was no seasonal variation.

I found the estimate of the prevalence of UTI, defined as the growth of one organism of greater than 100,000 cfu/ml, in acutely ill children under five years old to be 5.9% (35/597) with a 95% confidence interval of 4.3-8.0%.

Culture results

In addition to the prevalence of UTI defined as the growth of one organism of greater than 10^5 cfu/ml (primary outcome: 5.9%), I was also interested in borderline culture results. I considered these to be either the growth of a single organism of between 10^4 and 10^5 cfu/ml (11/597;1.8%) or the growth of two organisms of more than 100,000 cfu/ml (6/597; 1.0%). In total, a further 2.8% were considered to have a borderline result (see Table 5.11).

Almost half of the samples (48.4%) had mixed growths, presumed to be contaminants, and regarded as negative. The standard definition of UTI (used for this study) requires there to be a pure or predominant growth of a single organism. A culture result of mixed growth or heavy mixed growth, does not meet the criteria required for a UTI. It is therefore regarded as 'not-UTI'. Clinicians may treat choose to repeat the culture on another urine sample or may treat it as negative. However, it is possible that contaminating bacteria are hiding a true UTI (false negative result) or that the UTI is caused by more than one organism. If either of these cases were true, the prevalence of UTI found in my study would be an underestimation of the true prevalence.

Heavy mixed growths were more common in nappy pad samples (61.7%) compared with clean catch samples (13.2%; $p>0.01$). Forty (6.7%) urine samples were not cultured as microscopy was negative.

Table 5.11: Culture results

Culture result		Number (%)	% (95% CI)
Positive	$>10^5$ cfu/ml single organism	35 (5.9)	**5.9** (4.3-8.0)
Borderline	10^4-10^5 cfu/ml single organism	11 (1.8)	**2.8** (1.8-4.5)
	$>10^5$ cfu/ml two organisms	6 (1.0)	
Negative	Heavy mixed growth $>10^5$ cfu/ml	208 (34.8)	**91.3** (88.8-93.3)
	Mixed growth 10^4-10^5 cfu/ml	81 (13.6)	
	No growth or growth $<10^4$ cfu/ml	216 (36.2)	
	Not cultured as microscopy negative	40 (6.7)	

Overall, more than half (54.2%) of the UTIs were caused by *E.coli*. About a fifth (22.9%) were reported as Coliform, and a further fifth as other organisms. Further data regarding bacterial species and sensitivity profile is given later in the chapter along with antibiotic prescription and outcomes.

Prevalence of UTI by age and gender

Although age was not statistically significantly associated with UTI at the p=0.05 level, there was a trend towards a higher prevalence of UTI in the younger children (p=0.05; Table 5.12). The sample size was small and confidence intervals were wide in the youngest children, suggesting that the study was underpowered to detect a difference.

There was no significant difference in the prevalence of UTI between girls and boys, with 19/284 (6.7%) of girls and 16/313 (5.1%) of boys with UTI (p=0.41). Table 5.13 gives a breakdown of the association between gender and UTI by age. There was no difference in the gender of children with UTI aged less than three years, but UTI was more common in girls than boys over the age of three years (p<0.01).

Table 5.12: Prevalence of UTI by age

Age range (NICE)	Proportion with UTI	% UTI	95% CI
<3 months	4/32	12.5%	5-28%
≥3 months & <3 years	24/349	6.9%	5-10%
≥3 years	7/216	3.2%	2-7%
Total	35/597	5.9%	4-8%

p=0.05

Table 5.13 Prevalence of UTI by age and gender combined

Age range (NICE)	Gender	UTI (%)	p-value (Fisher's exact)
< 3 mths	Male	2/18 (11.1%)	1.00
	Female	2/14 (14.3%)	
≥3 mths & <3 yrs	Male	14/177 (7.9%)	0.53
	Female	10/172 (5.8%)	
≥3 yrs	Male	0/118 (0.0%)	**<0.01**
	Female	7/98 (7.1%)	

Urine sampling method and UTI prevalence

The method of urine collection was indicated in 431 (72.2%) children. Table 5.14 shows the proportion of UTIs with each method. Table 5.15 shows the proportion of UTIs by sample method and age.

Overall, there seemed to be a higher proportion of UTIs in those whose urine was collected using the nappy pad method, although this difference was not statistically significant (p=0.19; Table 5.14).

Table 5.14: urine sampling method and association with UTI

Urine sampling method	n	%UTI
Clean catch	232	3.0%
Nappy pad	199	5.5%

p=0.19

Table 5.15: urine sample method and association with UTI by age

Age	Urine sample method	Proportion with UTI
≥ 3 years old	Clean catch	3/171 (1.8%)
	Nappy pad	0
<3 years old *	Clean catch	4/61 (6.6%)
	Nappy pad	11/199 (5.5%)

* p=0.76

However, when urine sample method was considered only in those less than three years old (the age group in whom both methods were used), the proportion of UTIs in the nappy pad

group was lower than in the clean catch group, although this difference was not statistically significant (p=0.76).

This suggests that the lower proportion of UTIs in clean catch samples overall may be mainly due to age rather than sampling method, with older children less likely to have UTI and more likely to have urine collected by the clean catch method.

Seasonal variation

Many common illnesses (e.g. URTI, Flu) are seasonal and I wanted to see whether there was a seasonal pattern to UTI. Table 5.16 shows recruitment and UTI prevalence by month.

Table 5.16: UTI prevalence by month

Month	Number recruited	Number with UTI (%)
January	31	2 (6.5%)
February	45	4 (8.9%)
March	69	3 (4.3%)
April	37	5 (13.5%)
May	43	0 (0.0%)
June	46	4 (8.7%)
July	53	3 (5.7%)
August	58	3 (5.2%)
September	57	3 (5.3%)
October	53	1 (1.9%)
November	60	5 (8.3%)
December	45	2 (4.4%)
Total	597	35 (5.9%)

The highest prevalence of UTI occurred in April but the lowest was in May. There did not appear to be a consistent pattern suggesting that a seasonal pattern for UTI is unlikely. Numbers were too small for statistical testing.

The numbers recruited (denominators) each month also do not show a pattern. I would have expected to see a peak in recruitment over the winter months reflecting increased presentation with other common illnesses. This does not convincingly show this.

Table 5.17: Year of recruitment

Year of recruitment	Number recruited	Number with UTI (%)
2008	230	7 (3.0%)
2009	258	16 (6.2%)
2010	109	12 (11.0%)
Total	**597**	**35 (5.9%)**

Table 5.17 shows the recruitment and prevalence of UTI by year.
There was a higher proportion of UTI diagnosed in 2010 than in 2008 or 2009 (p=0.01). In 2010, there were fewer practices still recruiting with fewer overall numbers recruited and two new practices with two new laboratories, which could potentially have influenced this.

Secondary Outcomes

Headline: a multivariable logistic regression model identified age range, pain or crying on passing urine and increased urinary frequency as being associated with UTI. A history of fever or absence of an alternative site of infection was not significantly associated with UTI.

Presenting symptoms
I wanted to examine whether presenting symptoms were associated with UTI and whether they could potentially be used to determine which children were more likely to have UTI or to target urine sampling.

As described in Chapter 4, missing data for presenting symptoms were considered not to have the symptom.

There were 7-11 children with missing data for runny nose, earache, cough, difficulty breathing, feverish, rash, irritable, clingy, low energy, poor sleep, poor feeding, diarrhoea, constipation and vomiting. There were more missing data (between 16-47 children) for sore

throat, muscle aches/pains, nausea, abdominal pain, colic, bed wetting, smelly urine, dark urine, dysuria, haematuria, poor urine flow, urinary frequency and poor weight gain.

Table 5.18 shows the presenting symptoms in those with UTI compared with those without UTI. Symptoms with a p-value of <0.1 on univariate analysis are highlighted in bold.

Table 5.18: Presenting symptoms in children with and without UTI

Symptom	Proportion of those with UTI with symptom (%)	Proportion of those without UTI with symptom (%)	p-value
Irritable/grouchy	**28/35 (80.0%)**	**355/562 (63.2%)**	**0.04**
Clingy	25/35 (71.4%)	376/562 (66.9%)	0.58
Poor feeding	24/35 (68.6%)	305/562 (54.3%)	0.10
Runny nose	23/35 (65.7%)	400/562 (71.2%)	0.49
Cough	23/35 (65.7%)	390/562 (69.4%)	0.65
Fever	21/35 (60.0%)	334/562 (59.4%)	0.95
Tiredness	20/35 (57.1%)	265/562 (47.2%)	0.25
Poor sleep	18/35 (51.4%)	297/562 (52.8%)	0.87
Sore throat	12/35 (34.3%)	218/562 (38.8%)	0.60
Increased urinary frequency	**11/35 (31.4%)**	**75/562 (13.3%)**	**< 0.01**
Vomiting	11/35 (31.4%)	16/562 (2.8%)	0.72
Smelly urine	11/35 (31.4%)	125/562 (22.2%)	0.21
Earache	10/35 (28.6%)	170/562 (30.2%)	0.83
Difficulty breathing	9/35 (25.7%)	133/562 (23.7%)	0.78
Abdominal pain	8/35 (22.9%)	115/562 (20.5%)	0.73
Dark urine	8/35 (22.9%)	78/562 (13.9%)	0.14
Rash	7/35 (20.0%)	120/562 (21.4%)	0.85
Nausea	5/35 (14.3%)	74/562 (13.2%)	0.80
Wetting when previously dry	**5/35 (14.3%)**	**32/562 (5.7%)**	**0.06**
Pain/crying when passing urine	**5/35 (14.3%)**	**26/562 (4.6%)**	**0.03**
Poor urine flow	3/35 (8.6%)	18/562 (3.2%)	0.12
Colic	2/35 (5.7%)	27/562 (4.8%)	0.68
Poor weight gain	1/35 (2.9%)	27/562 (4.8%)	1.00
Haematuria	1/35 (2.9%)	3/562 (0.5%)	0.22
Muscle aches or pains	**0/35 (0.0%)**	**55/562 (9.8%)**	**0.03**

Being irritable or grouchy, having an increased frequency of wet nappies or passing urine, pain or crying when passing urine and not having muscle aches or pains, were associated with UTI with a p-value of <0.05. A history of day or bed wetting when the child had previously been dry, was associated with UTI with a p-value of 0.06.

Signs

The signs which were recorded on the CRF included three continuous variables, which were temperature, pulse rate and respiratory rate, as well as a range of binary variables for examination findings.

For the continuous variables, in order to assess whether parametric (normal) or non-parametric parameters and tests would be more accurate, I needed to decide whether each variable had a normal distribution or not. I plotted histograms for each of these variables (Appendix 5.2). I have therefore presented parametric parameters and t-test for temperature and heart rate and non-parametric parameters and Mann Whitney U test for respiratory rate.

Table 5.19: Association of continuous variables with UTI.

Sign	n	Overall mean/median	S.d./IQR	UTI Mean/median	No UTI Mean/median	p-value
Temperature (measured in surgery; ^{o}C)	466	36.8 ^{o}C	0.97 (s.d.)	36.8 ^{o}C	36.9 ^{o}C	0.71
Pulse rate (beats per minute)	340	112	17.7 (s.d.)	109	112	0.46
Respiratory rate (breaths per minute)	304	28	12 (IQR)	27	28	0.67

There was no statistically significant difference in the values of these variables between children with and without UTI (Table 5.19). I also created a binary variable for temperature of $\geq$ 38.0^{o} C or <38.0^{o}C. There was a greater proportion of children with a temperature $\geq$ 38.0^{o} C in the UTI group (42.9%) compared with the non-UTI group (29.0%), with a p-value of 0.08.

Clinician examination findings

Table 5.20 shows the association of UTI with examination findings. There was no statistically significant difference in these examination findings between those with and those without UTI. Numbers of children who had positive examination findings overall were eight (1.3%) children with abnormal abdominal examination, 118 (19.8%) with abnormal throat examination, 75 (12.6%) with abnormal chest examination and 62 (10.4%) with abnormal ear examination. An abnormal ear examination was found in only 2.9% of children with UTI

compared with 10.9% of children without UTI, however this was not statistically significant (p=0.16).

Table 5.20: Examination findings and UTI

Examination/signs	No. of children with UTI positive for the finding (%)	No. of children without UTI positive for the finding (%)	p-value
Abdominal examination abnormal	1/35 (2.9%)	7/562 (1.2%)	0.39
Throat examination abnormal	7/35 (20.0%)	111/562 (19.8%)	0.97
Chest examination abnormal	4/35 (11.4%)	71/562 (12.6%)	1.00
Ear examination abnormal	1/35 (2.9%)	61/562 (10.9%)	0.16

Risk factors

Table 5.21 shows the association with other risk factors collected on the CRF with UTI.

Table 5.21: Association of risk factors with UTI.

Risk factor		Proportion of those with UTI with risk factor (%)	Proportion of those without UTI with risk factor (%)	p-value
Past history	Previous UTI	3/35 (8.6%)	31/562 (5.5%)	0.44
	Diabetes	0/35 (0.0%)	0/562 (0.0%)	-
	Asthma	**0/35**(0.0%)	**55/562 (9.8%)**	**0.06**
	Eczema	10/35 (28.6%)	104/562 (18.5%)	0.14
	Hypertension	0/35 (0.0%)	1/562 (0.2%)	1.00
	Kidney disease	**2/35 (5.7%)**	**5/562 (0.9%)**	**0.06**
	Circumcised	0/35 (0.0%)	8/562 (1.4%)	1.00
	Illnesses in past with fever but no obvious cause	9/35 (25.7%)	122/562 (21.7%)	0.58
	Any other illnesses	4/35 (11.4%)	73/562 (13.0%)	1.00
Birth history	Breast fed	20/35 (57.1%)	254/562 (45.2%)	0.17
	Abnormalities of renal system on A/N USS	2/35 (5.7%)	10/562 (1.8%)	0.15
	Antibiotics during pregnancy	6/35 (17.1%)	82/562 (14.6%)	0.68
Family history	UTI in childhood of brothers, sisters or parents	6/35 (17.1%)	114/562 (20.3%)	0.65
	Kidney disease	2/35 (5.7%)	30/562 (5.3%)	0.71

A past history of kidney disease was associated with UTI with a p-value of 0.06, but numbers were very small. A past history of asthma was more common in those without UTI (p=0.06). None of the other potential risk factors, including past history of UTI and family history of childhood UTI, were significantly associated with UTI. None of the boys who had UTI had been circumcised and only 8/313 (2.6%) of boys overall had been circumcised.

Anti-pyretics prior to consultation

More than half (55.6%) of parents indicated that their child had been given paracetamol in the 24 hours prior to the consultation. Both paracetamol and ibuprofen had been given in 15.6%. One third (34.6%) of children had not been given either paracetamol or ibuprofen. If it was not indicated that anti-pyretics were given on the CRF, I assumed that the child had not been given them. I looked at the association of having been given anti-pyretics with age of the child, a history of fever and association with UTI (Tables 5.22 and 5.23).

Table 5.22: Association of paracetamol in the 24 hours prior to the index consultation with age, history of fever and subsequent diagnosis of UTI

Variable		**Paracetamol in prior 24 hours**		**p-value**
		YES	**NO**	
Age	**<3 months**	7/32 (28.0%)	25/32 (72.0%)	P<0.01
	≥3 months & <3 years	200/349 (57.3%)	149/349 (42.7%)	
	≥ 3 years	125/216 (57.9%)	91/216 (42.1%)	
History of fever	**YES**	240/355 (67.6%)	115/355 (32.4%)	P<0.01
	NO	92/242 (38.0%)	150/242 (62.0%)	
UTI	**YES**	18/35 (51.0%)	17/35 (49.0%)	P=0.61
	NO	314/562 (55.9%)	248/562 (44.1%)	

Table 5.23: Association of ibuprofen in the 24 hours prior to the index consultation with age, history of fever and subsequent diagnosis of UTI

Variable		Ibuprofen in prior 24 hours		p-value
		YES	NO	
Age	< 3months	0/32 (0.0%)	32/32 (100.0%)	P=0.05
	≥3 months & <3 years	49/349 (14.0%)	300/349 (86.0%)	
	≥ 3 years	35/216 (16.2%)	181/216 (83.8%)	
History of fever	YES	71/355 (20.0%)	284/355 (80.0%)	P>0.01
	NO	13/242 (5.4%)	229/242 (94.6%)	
UTI	YES	4/35 (11.4%)	31/35(88.6%)	P=0.81
	NO	80/562 (14.2%	482/562 (85.8%)	

The youngest children (<3 months old) were less likely to have been given paracetamol (p<0.01) and ibuprofen (P=0.05). Children were more likely to have been given paracetamol and ibuprofen in the preceding 24 hours if they had had a history of fever described by the parents (p<0.01 for both paracetamol and ibuprofen). There was no association between paracetamol or ibuprofen with subsequent diagnosis of UTI (p=0.61 and p=0.81 respectively).

Assessment of illness

Parental and GP assessment of illness severity

Parents were asked to indicate how unwell they thought their child was using a 5 point scale from 0 (not unwell at all) to 4 (severely unwell). GPs were asked to assess children using a similar scale. Neither parents nor GPs graded any child as '4'. In order to analyse these variables more easily, the scales were re-coded into mild illness (scores of 0 and 1 combined) and moderate illness (scores of 2 and 3 combined).

This question was not answered by GPs and parents in 8 cases; missing from GPs in a further 21 and missing from parents in a further 32 cases.

Table 5.24 shows the comparison of parental and GP illness severity assessment scores.

Table 5.24: Association of parental and GP assessment of illness severity

		GP assessment		
		0-1 (mild illness)	**2-3 (moderate illness)**	**Total**
Parental assessment	**0-1 (mild illness)**	257(47.9%)	23(4.3%)	280 (52.2%)
	2-3 (moderate illness)	179(33.4%)	77(14.4%)	256 (47.8%)
	Total	436 (81.3%)	100 (18.7%)	536

p<0.01; Kappa=0.23

Parents assessed children to be more unwell than GPs (p<0.01) with 256 (47.8%) children assessed by parents as having a moderately severe episode compared with only 100 (18.7%) GPs. GPs and parents agreed on illness severity in 334 (62.3%) cases. The Kappa statistic (0.23) shows that overall there was fairly low agreement between GP's and parents' assessment of illness severity.

Tables 5.25 and 5.26 show the association of illness severity and UTI.

Both GPs and parents seemed to assess more children in the UTI group as having a greater severity of illness, however this was not statistically significant in either case (p=0.11 parents; p= 0.33 GPs). Considering an illness score of 2-3 by *either* parent *or* GP was not associated with UTI (p=0.27; Table 5.27) and neither was considering an illness score of 2-3 by *both* parent *and* GP (p=0.17; Table 5.27).

Table 5.25: Illness severity according to parent and association with UTI

		UTI		
		YES	**NO**	**Total**
Illness severity	**0-1**	12 (38.7%)	281 (53.4%)	293
	2-3	19 (61.3%)	245 (46.6%)	264
	Total	31	526	557

p=0.11

Table 5.26: Illness severity according to GP and association with UTI

		UTI		
		YES	**NO**	**Total**
Illness severity	**0-1**	24 (75.0%)	439 (81.9%)	463
	2-3	8 (25.0%)	97 (18.1%)	105
	Total	32	536	568

p=0.33

Table: 5.27: Illness severity by GP and Parent combined and association with UTI

		UTI		p-value
		YES	**NO**	
Illness severity score of 2-3 by either GP or parent	**YES**	18/279 (62.1%)	261/279 (51.2%)	P=0.27
	NO	11/257 (37.9%)	246/257 (48.5%)	
Illness severity score of 2-3 by both GP and parent	**YES**	7/77 (9.1%)	70/77 (90.9%)	P=0.17
	NO	22/459 (4.8%)	437/459 (95.2%)	

GP working diagnosis

Table 5.28 shows the GP working diagnosis and association with UTI. Of those with UTI (n=35), 14 (40%) were thought to have a URTI by GPs. UTI was found in 14 (7.9%) of children with a working diagnosis of URTI; in two (6.3%) diagnosed with tonsillitis; in seven (17.1%) of those thought to have UTI; and in three (8.3%) of those with no working diagnosis given. None of those diagnosed with LRTI (n=48) or ear infections (n=32) were found to have UTI.

Table 5.28: GP working diagnosis and UTI

GP working diagnosis	UTI (%)	No UTI (%)	Total
URTI	14 (7.9%)	163	177
LRTI	0 (0.0%)	48	48
Tonsillitis	2 (6.3%)	30	32
Ear infection	0 (0.0%)	32	32
Conjunctivitis	1 (6.7%)	14	15
Gastroenteritis	1 (3.8%)	25	26
UTI	7 (17.1%)	34	41
Viral illness	3 (3.3%)	87	90
Other	4 (4.0%)	96	100
No working diagnosis given/missing	3 (8.3%)	33	36
Total	**35**	**562**	**597**

I created two binary variables for statistical testing. One was 'suspected UTI'. GP suspicion of UTI was based on the 'working diagnosis' question on the CRF which was completed by GPs at the initial consultation and before urine culture results were available. The other binary variable I created was 'alternative source of infection' which I coded as positive if URTI, LRTI, tonsillitis, ear infection, conjunctivitis or gastroenteritis were given as a working diagnosis. If the working diagnosis given was UTI, viral illness, other or if it was missing, 'alternative source of infection' was coded as negative.

Table 5.29 shows association of suspected UTI with UTI on culture. A working diagnosis of UTI indicated by the GP was significantly associated with UTI on culture with an odds ratio of 4.0 ($p<0.01$). However, 80% of those with UTI on culture were not suspected of having UTI by GPs demonstrating that UTI in children is very difficult to diagnose clinically.

Table 5.29: Association of GP suspicion of UTI and UTI on culture

GP suspicion of UTI	UTI found on culture		Total	Odds
	YES	NO		
YES	7 (20.0%)	34 (6.0%)	41 (6.9%)	0.2
NO	28 (80.0%)	528 (94.0%)	556 (93.1%)	0.1
Total	35 (100%)	562 (100%)	597 (100%)	Odds ratio = 3.9

$p<0.01$

Table 5.30 shows the association of the presence of an alternative source of infection with UTI. This was not associated with UTI (p=0.64).

Table 5.30: Association of presence of an alternative source of infection and UTI

Presence of an alternative source of infection	UTI		Total
	YES	NO	
YES	18 (51.4%)	312 (55.5%)	330 (55.3%)
NO	17 (48.6%)	250 (44.5%)	267 (44.7%)
Total	35 (100%)	562 (100%)	597 (100%)

p=0.64

Predicting UTI

Multivariable analysis

Age category and symptoms or signs that were associated with UTI with a p-value of <0.1 on univariate analysis were entered into a forward stepwise logistic regression model (Table 5.31).

Although those with a UTI less commonly had a history of asthma (p=0.06), and more often had a history of kidney or bladder disease (p=0.06), past history was not included in the logistic regression model as I wanted to make the model as simple as possible, concentrating on clinical findings. Neither a history of fever described by parents nor an alternative site of infection (URTI, LRTI, tonsillitis, gastroenteritis, conjunctivitis, otitis) diagnosed by clinicians were significantly associated with UTI (p=0.95 and p=0.64 respectively) so these were not entered into the logistic regression model. No examination findings other than a fever of greater than or equal to 38^{o}C were associated with UTI. Table 5.31 shows the presenting symptoms and signs which were entered into the logistic regression model.

Table 5.31: Presenting symptoms and signs in children entered into the logistic regression model

Symptom	Proportion of those with UTI with symptom (%)	Proportion of those without UTI with symptom (%)	Odds ratio	p-value on univariable analysis
Increased urinary frequency	11/35 (31.4%)	75/562 (13.3%)	3.0	<0.01
Wetting when previously dry	5/35 (14.3%)	32/562 (5.7%)	2.8	0.06
Pain/crying when passing urine	5/35 (14.3%)	26/562 (4.6%)	3.4	0.03
Irritable/grouchy	28/35 (80.0%)	355/562 (63.2%)	2.3	0.04
Temp measured in surgery $\geq 38^{o}C$	15/35 (42.9%)	163/562 (29.0%)	1.8	0.08
Muscle aches or pains	0/35 (0.0%)	55/562 (9.8%)	0.1*	0.03
Poor feeding/off food	24/35 (68.6%)	305/562 (54.3%)	1.8	0.10

* Calculated using Yates' continuity correction.[175]

Multivariable analysis identified age range, pain or crying on passing urine and increased urinary frequency or frequency of wet nappies as being associated with UTI (Table 5.32).

Table 5.32: Multivariable analysis: variables included in the model

Symptom/characteristic	B	S.E.	95% CI for B		Odds ratio	p-value	95% CI for odds ratio
			Lower	Upper			
Urinary frequency	1.0	0.4	0.2	1.7	2.6	0.02	1.2-5.7
Pain on passing urine	1.2	0.6	0.2	2.3	3.3	0.03	1.1-9.8
NICE age range<3/12*	1.7	0.7	0.4	3.0	5.5	0.01	1.5-21.0
NICE age range 3/12-3 years*	0.9	0.5	0.0	1.7	2.4	0.06	1.0-5.8
Constant	-3.8	0.4	-4.6	-2.9			

Model χ^2 p <0.01; Nagelkerke R^2=0.08
* age range $\geq$3 years used as the reference range

Model fit

The model χ^2 is significantly different from the null model (the baseline model with the constant only and no predictors), with a p-value of <0.01, suggesting that UTI prediction is improved based on these symptoms and signs. However, the Nagelkerke R^2 statistic (0.08) implies that the model is not a very good fit.

Predicted probability of UTI based on the model

Headline: Using the multivariable model, the estimated probability of UTI in children less than three years old was >5% irrespective of presenting symptoms and signs. In children aged three to five years old, with neither pain on passing urine nor increased urinary frequency, the estimated probability of UTI was 2%. A proposed urine sampling strategy based on this model would detect 97% of UTIs but would involve a large increase in urine sampling from acutely ill children.

I wanted to calculate the probability of UTI for children of different age groups presenting with or without the symptoms in the model (summarised in Table 5.32). My calculations are shown in Appendix 5.3. I have summarised the probabilities and confidence intervals in tables 5.33-5.35.

Table 5.33: Predicted probability of UTI (with 95% confidence intervals) for children aged less than 3 months with and without urinary frequency and dysuria.

Age <3 months		**Pain/crying on passing urine % (95% CI)**	
		YES	**NO**
Increased frequency of urine/wet nappies	**YES**	31.5% (5.4-98.4)	25.3% (1.7-86.4)
	NO	29.4% (4.5-91.5)	10.4% (1.4-52.5)

All of the probabilities have wide confidence intervals. If there is pain/crying on passing urine, it is unlikely that the true probability lies below 4.5%, even with the wide confidence intervals, irrespective of increased urinary frequency. If there is no pain/crying on passing urine, the lower confidence interval drops to 1.4%.

Table 5.34: Predicted probability of UTI (with 95% confidence intervals) for children aged 3 months or more but less than 3 years with and without urinary frequency and dysuria.

Age ≥ 3 mths & <3 yrs		**Pain/crying on passing urine (95% CI)**	
		YES	**NO**
Increased frequency of urine/wet nappies	**YES**	32.0% (3.8-94.4%)	15.2% (1.2-63.4%)
	NO	12.5% (3.2-74.7%)	5.1% (1.0-23.2%)

All of the probabilities have wide confidence intervals. If there is pain/crying on passing urine, it is unlikely that the true probability lies below 3.2%, irrespective of increased urinary frequency. If there is no pain/crying on passing urine, the lower confidence interval drops to 1.0%.

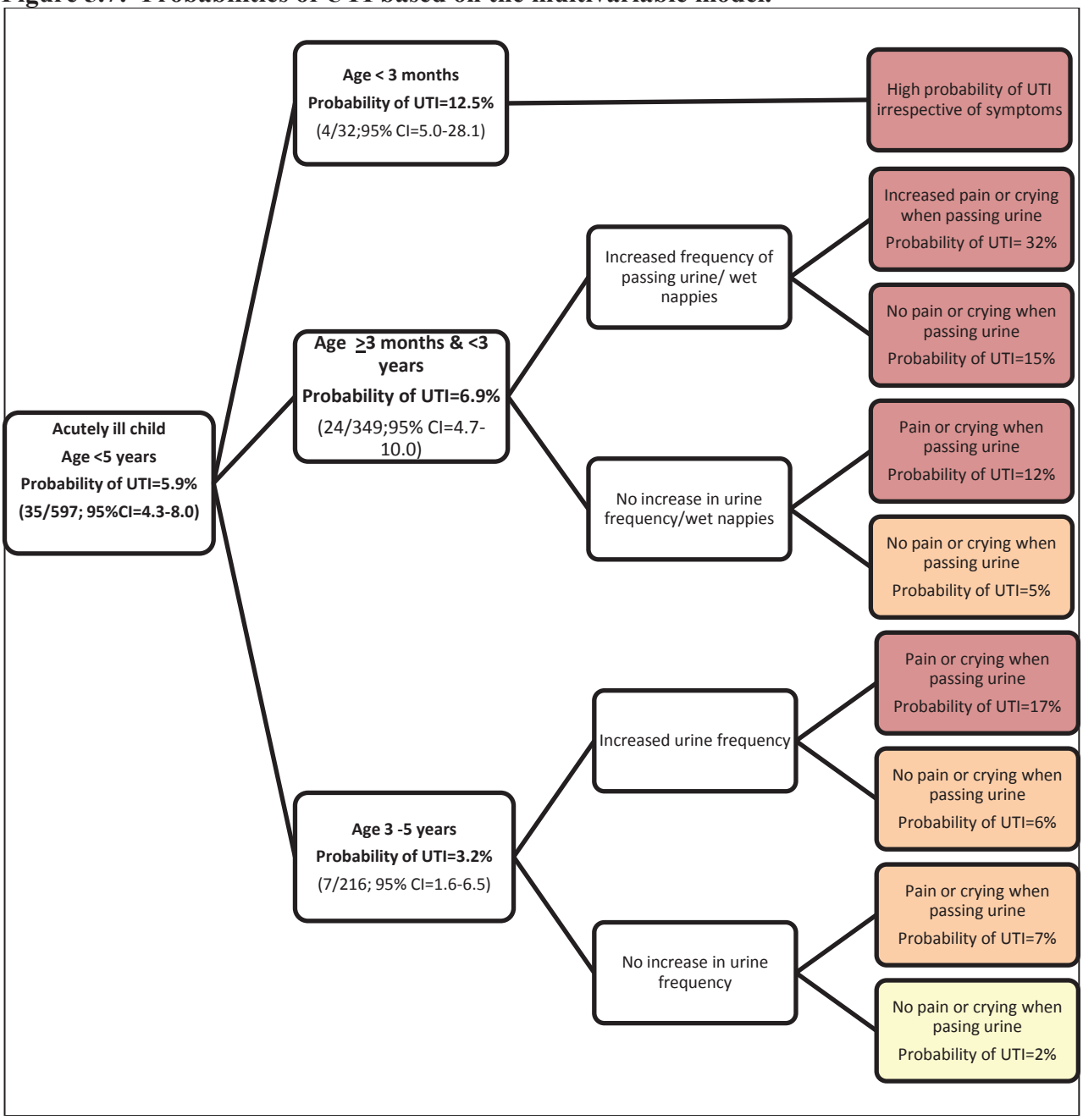
Table 5.35: Predicted probability of UTI (with 95% confidence intervals) for children aged 3 years or more with and without urinary frequency and dysuria.

Age ≥ 3yrs		**Pain/crying on passing urine (95% CI)**	
		YES	**NO**
Increased frequency of urine/wet nappies	**YES**	16.5% (5.4-74.7%)	5.7% (1.7-23.2%)
	NO	6.7% (4.5-34.0%)	2.2% (1.0-5.0%)

All of the probabilities have wide confidence intervals. If there is pain/crying on passing urine, it is unlikely that the true probability lies below 4.5% (the lower confidence interval), even with the wide confidence intervals, irrespective of increased urinary frequency. If there is no pain/crying on passing urine, the lower confidence interval drops to 1.0%.

These probabilities are summarised in Figure 5.7, presented to nearest whole percentage for the figure. I have highlighted low probabilities of UTI in yellow, high probabilities in red and those with moderate probabilities in orange.

Figure 5.7: Probabilities of UTI based on the multivariable model.



- In children younger than 3 months, the probability of UTI was high, irrespective of symptoms, at 12.5% with 95% confidence interval of 5.0%-28.1%.
- In children 3 months or older but less than 3 years old, the overall prevalence was 6.9% with a 95% confidence interval of 4.7%-10.0%.
- Looking more closely at the symptoms based on the model, the highest probability of UTI is in children with increased frequency of passing urine (or number of wet nappies), particularly if they also have pain or crying when passing urine. Children in this age group, with neither pain/crying on passing urine nor increased urinary

frequency, had a probability of UTI of 5% but the 95% confidence intervals are wide (1.0%-23.2%).

- For children aged 3-5 years, the overall probability of UTI was 3.2% with a 95% confidence interval of 1.6%-6.5%. The probability was highest if both dysuria and frequency were present (17%; 95% CI 5.4%-74.7%), approximately 6%-7% if only one of the symptoms were present, but much lower if neither were present, with a probability of 2% (95% CI 1.0%-5.0%).

Urine sampling strategies

Several urine sampling strategies are available to GPs. One option is to sample urine only when UTI is suspected. Another strategy would be to follow the NICE guideline recommendations for urine sampling.[1] Another sampling strategy would be to sample urine from all presenting ill children less than five years old. Based on the results of this study, I propose another possible sampling strategy:

As confidence intervals are wide, caution is needed for making recommendations. However, one possible strategy may be to sample urine from all children aged less than three years, and in children aged between three and five years who have either urinary frequency or dysuria (or both), but not to sample urine from children aged between three and five years with neither urinary frequency nor dysuria.

Comparison of various sampling strategies

In the next section I compare four sampling strategies with culture results to determine the sensitivity and specificity of using each method to determine which children should have their urine sampled:

1) Urine sampling based on GP suspicion of UTI
2) Urine sampling based on the NICE guidelines
3) Sampling urine from all children less than three years old and in children aged between three and five years old with urinary frequency or dysuria (proposed urine sampling strategy).
4) Universal urine sampling from all acutely ill children <5 years old.

Urine sampling based on GP suspicion of UTI

GP suspicion of UTI was based on the 'working diagnosis' question on the CRF which was completed by GPs at the initial consultation and before urine culture results were available. A working diagnosis of UTI indicated by the GP was significantly associated with UTI on culture with an odds ratio of 3.9 ($p<0.01$; Table 5.29). However, the sensitivity is only 20% (Table 5.3). This means that 80% of UTIs found on culture would have been missed if only those who were suspected of having UTI had their urine sampled.

Table 5.36: Predictive value of GP suspicion of UTI

Feature	Value	
Sensitivity	7/35	20.0%
Specificity	528/562	94.0%

Urine sampling based on the NICE guidelines[1]

Figures 5.8 and 5.9 show the summary of guidance for diagnosis of UTI copied directly from the NICE guideline.

Figure 5.8: Summary of guidance for diagnosis section 1.1:

1.1 Diagnosis

1.1.1 Symptoms and signs

- Infants and children presenting with unexplained fever of 38°C or higher should have a urine sample tested after 24 hours at the latest.

- Infants and children with an alternative site of infection should not have a urine sample tested. When infants and children with an alternative site of infection remain unwell, urine testing should be considered after 24 hours at the latest.

- Infants and children with symptoms and signs suggestive of urinary tract infection (UTI) should have a urine sample tested for infection. Table 1 is a guide to the symptoms and signs that infants and children present with.

Figure 5.9: Presenting symptoms and signs in infants and children with UTI from NICE

Age group		**Symptoms and signs** Most common ⟶ Least common		
Infants younger than 3 months		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Infants and children, 3 months or older	**Preverbal**	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

I used Figures 5.8 and 5.9 to calculate which children would have had a urine sample sent if the NICE guidelines had been followed. I assumed that one of any of the symptoms given would be sufficient to warrant a urine sample. If there was an alternative site of infection, a urine sample was not deemed necessary.

Table 5.37: Urine sampling based on NICE guidelines and UTI

Sample based on NICE guidelines	**UTI found on culture**		**Total**	**Odds**
	YES	**NO**		
YES	17 (48.6%)	219 (39.0%)	236 (39.5%)	0.08
NO	18 (51.4%)	343 (61.0%)	361 (60.5%)	0.05
Total	35	562	597	Odds ratio=1.5

Sensitivity = 17/35 = 48.6%; Specificity=343/562=61.0%

Many more children (six fold) would have their urine sampled if the NICE guidelines were followed compared with sampling based on GP suspicion (Table 5.37). The sensitivity is higher, detecting twice as many UTIs. Urine would be sampled in 40% children using this strategy but would still miss 51% of UTIs.

Proposed urine sampling strategy

Table 5.38 summarises the association of culture results with urine sampling using my proposed strategy, where urine is sampled from all children less than three years old and only in children three years or older if they have urinary frequency or dysuria.

Table 5.38: Association of culture results with proposed urine sampling strategy

Urine sample based on proposed urine sampling strategy	**UTI found on culture**		**Total**	**Odds**
	YES	**NO**		
YES	34 (97.1%)	380 (67.6%)	414 (69.3%)	0.09
NO	1 (2.9%)	182 (32.4%)	183 (30.7%)	0.01
Total	35	562	597	Odds ratio = 16.3

Sensitivity = 34/35 = 97.1%; Specificity = 182/562 = 32.4%

Comparing the proposed sampling method with sampling based on NICE guidelines

Only one (2.9%) of those with UTI would have been missed with the proposed sampling method, giving a sensitivity of 97.1%. Urine samples would need to be obtained in 69.3% of children (compared with 39.5% with the NICE guidelines). This increase in urine sampling (1.8 fold) would result in double the number of UTIs detected (97.1% vs. 48.6%).

Comparing the proposed sampling method with sampling based on GP suspicion

Comparing the proposed sampling method with sampling based on GP suspicion, 10 times more urine samples would be needed but five times more UTI would be detected.
With this sampling strategy, 12 urine samples need to be sampled and tested to pick up one UTI (number needed to test=12).

Comparing the proposed sampling method with universal sampling

Comparing the proposed sampling method with a universal sampling strategy, 183 less samples would be needed (30% less), but one UTI would be missed.

The one child missed using my proposed sampling method and my dataset was a four year old girl with no urinary symptoms but with abdominal pain and vomiting and a past history of UTI. The GP did not give a working diagnosis.

Table 5.39 compares the proposed sampling strategy with sampling based on GP suspicion, NICE guidelines and universal sampling.

Table 5.39: Urine sampling outcomes based on GP suspicion, NICE guidelines, universal sampling and a proposed sampling strategy based on the model.

Age group	Urine sample	GP suspicion	If NICE guidelines had been applied	Universal sampling (all acutely ill children <5 years)	Proposed sampling strategy
<3 months (n=32)	Number urine samples	0	9	32	32
	Number UTI diagnosed	0	1	4	4
	Number UTI missed	4	3	0	0
3 mths-3 yrs (n=349)	Number urine samples	19	150	349	349
	Number UTI diagnosed	3	10	24	24
	Number UTI missed	21	14	0	0
≥3 yrs (n=216)	Number urine samples	22	77	216	33
	Number UTI diagnosed	4	6	7	6
	Number UTI missed	3	1	0	1
TOTAL	**Number urine samples**	**41 (6.9%)**	**236 (39.5%)**	**597 (100.0%)**	**414 (69.3%)**
	Number UTI diagnosed	**7 (20.0%)**	**17 (48.6%)**	**35 (100.0%)**	**34 (97.1%)**
	Number UTI missed	**28 (80.0%)**	**18 (51.4%)**	**0 (0.0%)**	**1 (2.9%)**
	Sensitivity	20.0%	48.6%	100.0%	97.1%
	Specificity	94.0%	61.0%	0.0%	32.4%

Near patient testing

Urinary dipsticks

Headline: Nitrites and blood on urinary dipstick were associated with UTI. However, sensitivity was low (<50% in each case). Specificity was high (97.2%) when both leukocytes and nitrites were positive. Dipstick findings varied by urine sampling method.

Predictive symptoms or signs can be used to help to determine which children should have their urine sampled, as described above. Once the urine has been obtained, the next decisions are: whether the sample should be sent to the laboratory for microscopy and culture or not and whether the child should be treated with immediate antibiotics or not.

Urine dipsticks are frequently used in adults, and in practice are probably often used in children. However, the reliability of the use of dipsticks in children has been questioned, as discussed in chapter 1.[1 112]

The children in my study may be different from previously studied populations of children as these children have had their urine systematically sampled for presentations of all acute illnesses. Therefore, I wanted to examine the predictive value of the dipsticks in my population, despite the fact that my study was not powered to determine these with great accuracy.

Of the 597 included in the main analysis, 397 (66.5%) had dipstick results. Table 5.40 shows the urinary dipstick tests which were found to be significantly associated with UTI.

Table 5.40: Testing an association between dipsticks and UTI

Dipstick test	**Association with UTI: p-value**
Leukocytes	0.08
Nitrites	**<0.01**
Protein	0.38
Blood	**0.04**
Ketones	0.13
Glucose	0.12

Leukocytes were not found to be significantly associated with UTI. However, as this is commonly used as a predictor for UTI I have included it in Table 5.41. I have also included combinations of positive findings of leukocytes and nitrites as these have been combined and used in algorithms previously and are advised by NICE for children aged three years or older.[1]

Table 5.41: Dipstick results and association with UTI

Positive on Urine dipstick test for:	UTI (%)	No UTI (%)	p-value	Sensitivity	Specificity
Leukocytes	5/16 (31.3%)	52/359 (14.5%)	P=0.08	31.3%	85.5%
Nitrites	7/16 (43.8%)	21/359 (5.8%)	P<0.01	43.8%	94.2%
Blood	4/16 (25.0%)	28/359 (7.8%)	P=0.04	25.0%	92.2%
Both Leukocytes AND Nitrites positive	4/16 (25.0%)	10/359 (2.8%)	P<0.01	25.0%	97.2%
Either Leukocytes OR Nitrites positive	8/16 (50.0%)	63/359 (17.5%)	P<0.01	50.0%	82.5%

All of the dipstick tests are fairly specific but all have very low sensitivity. So, using them to diagnose UTI would result in many cases of UTI being missed. One option may be to use them to treat some children with antibiotics whilst waiting for the culture result. With a high specificity this would not result in many unnecessary antibiotics, but would mean that most UTI would not be treated until the culture result became available.

Dipstick findings: urine sampling method and age

I wanted to explore dipstick findings with different urine sampling methods as this has not been established clearly in previous studies. Table 5.42 compares dipstick findings with the two different urine sampling methods.

Table 5.42: Dipstick findings and urine sampling method

Dipstick test	Number (%) of clean catch samples which are positive for the test	Number (%) of nappy pad samples which are positive for the test	p-value
Leukocytes	27 (12.4%)	30 (19.4%)	0.05
Nitrites	8 (3.7%)	20 (12.9%)	<0.01
Protein	55 (25.2%)	18 (11.6%)	<0.01
Blood	22 (10.1%)	10 (6.5%)	0.15
Ketones	36 (16.5%)	12 (7.7%)	0.01
Glucose	0 (0.0%)	3 (1.9%)	0.07

Protein and ketones were less commonly found in nappy pad samples compared with clean catch samples Nitrites were more commonly positive in nappy pad samples. This is interesting as the rates of UTI were similar in nappy pad and clean catch samples.

One possible explanation is that the age of the child may be confounding this association. Table 5.43 shows the proportion of positive dipstick findings by age. There are higher levels of nitrites in younger children and higher levels of protein and ketones in older children.

Table 5.43: Dipstick results and age

Dipstick	Number (%) of <3 month olds positive for the test	Number (%) of 3mths-3yrs positive for the test	Number (%) of >3 yr olds positive for the test	p-value
Leukocytes	5 (25.0%)	34 (17.7%)	18 (11.0%)	0.10
Nitrites	4 (20.0%)	22 (11.5%)	2 (1.2%)	<0.01
Protein	2 (10.0%)	25 (13.0%)	46 (28.2%)	0.01
Blood	3 (15.0%)	13 (6.8%)	16 (9.8%)	0.34
Ketones	1 (5.0%)	18 (9.4%)	29 (17.8%)	0.03
Glucose	1 (5.0%)	2 (1.0%)	0 (0.0%)	*

* Numbers too small for χ^2 test

Clinical outcomes

Headline: Antibiotics were prescribed at the index consultation in 28.3% of children overall and in 37.1% of those with UTI. Children with UTI were more likely to have received an appropriate antibiotic at the index consultation if the GP's working diagnosis included UTI. Half of the children with UTI had an illness which lasted more than two weeks. There was no difference in the number of re-consultations, admission or hospital referrals between those with and without UTI at six month follow-up. Children with a UTI received more courses of oral antibiotics in the following six months than children without UTI. Adherence to NICE guidelines for imaging following UTI was low (3.6%).

Initial management

Antibiotic prescription

Oral antibiotics were prescribed at the initial (index) consultation in 169 (28.3%) children (Table 5.44). The majority of antibiotic prescriptions were for respiratory tract infections, with lower respiratory tract infections (LRTI) accounting for 24.0% of all antibiotic prescriptions and upper respiratory tract infections (URTI) accounting for a further 19.2%. Antibiotics were prescribed in 90.6% cases of tonsillitis, in 83.3% of LRTI and in 75.0% of ear infections (Table 5.45). Approximately half of those with a working diagnosis of UTI were prescribed antibiotics at the index consultation (prior to the diagnosis being confirmed with culture results).

Table 5.46 shows the association of GP working diagnosis and oral antibiotic prescription at index consultation where the GP working diagnoses were amalgamated into fewer categories to allow statistical testing. This shows that there was a statistically significant difference in oral antibiotic prescription according to GP working diagnosis ($p<0.01$).

Table 5.45: Antibiotic prescription at index consultation and GP working diagnosis

Oral antibiotics at index consultation	GP working diagnosis									
	URTI	LRTI	Tonsillitis	Ear infection	Conjunctivitis	Gastroenteritis	UTI	Viral illness	Other	Total
Yes	32 (18.1%)	40 (83.3%)	29 (90.6%)	24 (75.0%)	0 (0.0%)	1 (3.8%)	21 (51.2%)	6 (6.7%)	14 (14.0%)	167
No	145 (81.9%)	8 (16.7%)	3 (9.4%)	8 (25.0%)	15 (100.0%)	25 (96.2%)	20 (48.8%)	84 (93.3%)	86 (86.0%)	394
Total	177	48	32	32	15	26	41	90	100	561*

*no working diagnosis listed in 36

Table 5.46: GP working diagnosis in 5 categories

Oral antibiotics at index consultation	GP working diagnosis					
	Respiratory tract infections	Ear infections	UTI	Other illnesses	No working diagnosis given	Total
Yes	101(39.3%)	24 (75.0%)	21(51.2%)	21(9.1%)	2 (5.6%)	169 (28.3%)
No	156 (60.7%)	8 (25.0%)	20 (48.8%)	210 (90.9%)	34 (94.4%)	428 (71.7%)
Total	257	32	41	231	36	597

$p<0.01$

GPs were twice as likely to prescribe antibiotics at the index consultation if their working diagnosis included UTI (51.2% vs. 26.6%; p<0.01; Table 5.47).

Table 5.47: Comparing antibiotic prescription at index consultation in those with and without a working diagnosis of UTI

Oral antibiotic prescription at index consultation	GP working diagnosis includes UTI	UTI not listed in GP working diagnosis	Total
Oral antibiotics prescribed	21 (51.2%)	148 (26.6%)	169 (28.3%)
Oral antibiotics not prescribed	20 (48.8%)	408 (73.4%)	428 (71.7%)
Total	41	556	597

p<0.01

A higher GP illness severity score was associated with an increased likelihood of prescription of antibiotics (p<0.01; Table 5.48).

Table 5.48: GP assessment of illness severity and association with prescription of antibiotics at the index consultation

Oral antibiotics prescribed	GP illness severity score		
	0-1	**2-3**	**Total**
Yes	107(23.1%)	60 (57.1%)	167 (29.4%)
No	356 (76.9%)	45 (42.9%)	401 (70.6%)
Total	463	105	568*

* missing information in 29

p<0.01

A child with a temperature of 38^{o}C or more measured in the surgery increased the likelihood of an antibiotic prescription at the index consultation. However, only 36.0% of those with a temperature of 38^{o}C or more were prescribed an antibiotic (p<0.01; Table 5.49).

Table 5.49: Fever of 38°C or more measured in surgery and association with antibiotic prescription

Oral antibiotics prescribed	Temperature measured in surgery		Total
	≥38°C	<38°C	
Yes	64 (36.0%)	105 (25.1%)	169 (28.3%)
No	114 (64.0%)	314 (74.9%)	428 (71.7%)
Total	178	419	597

p<0.01

Association of antibiotic prescription and subsequent UTI

Table 5.50 shows that antibiotics were prescribed at the initial (index) consultation in 37.1% of those who were subsequently found to have a UTI and in 27.8% of those who were subsequently found not to have a UTI, but the difference was not statistically significant (p=0.23).

Table 5.50: Antibiotic prescription at index consultation and association with UTI

Oral antibiotic prescription at index consultation	Subsequent culture result		
	UTI	No UTI	Total
Oral antibiotics prescribed	13 (37.1%)	156 (27.8%)	169 (28.3%)
Oral antibiotics not prescribed	22 (62.9%)	406 (72.2%)	428 (71.7%)
Total	35	562	597

p=0.23

14 day follow-up

Illness duration

Telephone follow up was completed on 28/52 (57%) children with a positive or borderline culture result two weeks following index consultation. In 17 cases the urine result was not available in time to do the telephone follow up. In seven cases there was no answer despite multiple attempts.

Table 5.51 shows the outcomes for the 18 children with UTI and the ten children with borderline culture results who had telephone follow up completed.

Table 5.51: 14 day outcomes for children with UTI

14 day outcome	UTI	Borderline culture results
Telephone follow up completed	**18**	**10**
Child had fully recovered from illness	9 (50.0%)	7 (70.0%)
Illness lasted >2 weeks	9 (50.0%)	3 (30.0%)
Child had been assessed or admitted to hospital	0 (0.0%)	0 (0.0%)
Child had re-consulted with GP	3 (16.7%)	2 (20.0%)
Child had re-consulted with nurse	1 (5.6%)	0 (0.0%)
Child had been to A&E	0 (0.0%)	0 (0.0%)
Child had been seen in OOH	2 (11.1%)	0 (0.0%)
Advice had been sought from pharmacist	0 (0.0%)	1 (10.0%)
Advice had been sought from NHS Direct	1 (5.6%)	0 (0.0%)
Child had been to see a specialist	0 (0.0%)	1 (10.0%)

Of the nine children with UTI who had not fully recovered by two weeks, two (22.2%) had been prescribed antibiotics at the initial consultation (one was prescribed trimethoprim and one was prescribed amoxicillin). Two of the nine children (22.2%) who had fully recovered within two weeks were also prescribed antibiotics at the initial consultation (one had been prescribed cefalexin and one was prescribed penicillin V).

Six month follow-up

Of those included in the main analysis, 515 follow-up forms were sent to practices and returned, completed; four were sent and not completed due to the patients leaving the

practice. A total of 78 were not sent follow up forms to complete due to urine results not being available until later.

The following results relate to those included in the main analysis with completed six month follow up forms (n=515).

Table 5.52: Six month outcomes comparing those with UTI and those without

Variable		Frequency in those with UTI at index consultation	Frequency in those with negative culture at index consultation	p-value
Number of in surgery face to face consultations	**0-1**	8 (28.6%)	189 (38.8%)	0.28
	≥2	20 (71.4%)	298 (61.2%)	
Number of acute/same day hospital admissions	**0**	27 (96.4%)	452 (92.8%)	0.40
	≥1	1 (3.6%)	35 (7.2%)	
Number of OOH or A+E contacts (including telephone)	**0**	14 (50.0%)	315 (64.7%	0.12
	≥1	14 (50.0%)	172 (35.3%)	
Number of courses of oral antibiotics	**0**	7 (25.0%)	243 (49.9%)	**0.02**
	1	11 (39.3%)	154 (31.6%)	
	≥2	10 (35.7%)	90 (18.5%)	
Number of children referred to the hospital for any reason		6 (21.4%)	50 (10.3%)	0.10
Number of children referred for or had any investigations of the renal tract		4 (14.3%)	7 (1.4%)	**<0.01**
Number of children who have had or been referred for an USS		3 (10.7%)	6 (1.2%)	**0.01**
Number of children who have had or been referred for a DMSA scan		1 (3.6%)	1 (0.2%)	0.07
Number of children who have had or been referred for a MCUG scan		0 (0.0%)	0 (0.0%)	
Total		**28**	**487**	

Table 5.52 shows outcome variables for the 6 months following the index consultation for those with UTI compared to those without. There were more referrals for renal tract investigations ($p<0.01$) and ultrasound scans ($p=0.01$). This is an expected finding as

guidelines recommend investigations and ultrasound scans for some children with UTI. Out of the 28 children with UTI in whom follow up data are available, three (10.7%) had been referred for or had an USS in the following six months, one (3.6%) had had or been referred for a DMSA scan and no children had had or been referred for a MCUG scan.

The numbers were small when those with borderline results were considered separately and no statistical testing was performed. Eleven (64.7%) had two or more face to face consultations during the six month period; one (5.9%) had one or more hospital admissions; seven (41.2%) had one or more OOH/A&E contacts; and two (11.8%) had two or more courses of oral antibiotics. Two children with borderline results (11.8%) had been referred to hospital, and had been referred for or received ultrasound scans of the renal tract.

There was a significant difference in the number of courses of antibiotics in the following six months between those with UTI and those without (p=0.02). Twice as many children with a UTI received two or more courses of antibiotics in the following six months compared with children without a UTI.

Causative organism, antimicrobial sensitivity profile and empirical antibiotics

Table 5.53 shows the antimicrobial sensitivity profile of the organism causing UTI and the antibiotic which was prescribed for children suspected and not suspected of having a UTI.

Table 5.53 Causative organism, antimicrobial sensitivity profile and prescribed antibiotics for children with UTI

	PID	Name of organism	Antibiotics to which the organism is resistant	Antibiotic prescribed at index consultation	Was prescribed antibiotic likely to treat UTI?
GP suspected UTI (n=7)	326	Coliform	Not given	Trimethoprim	Unclear
	1337	*E.coli*	Fully sensitive	Cefalexin	Yes
	363	Coliform	Amoxicillin	None	No
	1823	*E.coli*	Amoxicillin	Trimethoprim	Yes
	1055	Coliform	Fully sensitive	Trimethoprim	Yes
	1154	*E.coli*	Amoxicillin	Trimethoprim	Yes
	1851	*E.coli*	Amoxicillin, Trimethoprim	Augmentin	Yes
GP did not suspect UTI (n=28)	463	*E.coli*	Fully sensitive	None	No
	468	*E.coli*	Amoxicillin, Co-amoxiclav	Penicillin V	No
	1938	*E.coli*	Amoxicillin, Co-amoxiclav	Amoxicillin	No
	1153	*Enterococcus*	Fully sensitive	None	No
	39	Coliform	Not given	None	No
	1085	*E.coli*	Amoxicillin	None	No
	461	*E.coli*	Amoxicillin, Co-amoxiclav	Amoxicillin	No
	472	*E.coli*	Amoxicillin	Penicillin V	No
	396	*E.coli*	Fully sensitive	None	No
	1361	*E.coli*	Amoxicillin	None	No
	1832	*Citrobacter freundii*	Amoxicillin, Cefalexin	None	No
	1342	*Coag neg staph**	Fully sensitive	None	No
	1368	*Enterococcus*	Fully sensitive	None	No
	1377	*E.coli*	Amoxicillin	Amoxicillin	No
	1383	*E.coli*	Fully sensitive	None	No
	2019	*Enterococcus cloacae*	Not given	None	No
	1029	Coliform	Trimethoprim	None	No
	1077	*Coag neg staph**	Fully sensitive	None	No
	156	Coliform	Not given	None	No
	158	Coliform	Not given	None	No
	408	*Staphylococcus*	Not given	None	No
	1685	Coliform	Amoxicillin, Augmentin, Nitrofurantoin	None	No
	2016	*E.coli*	Ampicillin, Co-amoxiclav, Trimethoprim	None	No
	2063	*E.coli*	Not given	Amoxicillin	Unclear
	1382	*Coag neg staph**	Fully sensitive	Co-amoxiclav	Yes
	5002	*E.coli*	Fully sensitive	None	No
	3003	*E.coli*	Fully sensitive	None	No
	2057	*E.coli*	Fully sensitive	None	No

** Coagulase negative staphylococcus*

Of the seven who the GP suspected of having a UTI, six were prescribed an antibiotic. In five of these cases the bacteria was listed by the laboratory as showing sensitivity to the antibiotic prescribed. In one case sensitivities were not given by the laboratory.

Of the 28 not suspected of having a UTI by the GP, antibiotics were prescribed in seven cases. However, in most of these cases (five) the antibiotic prescribed was one to which the bacteria were resistant (based on the laboratory report). In one case the bacteria were listed as being sensitive to the antibiotic prescribed, and in one case sensitivities were not provided. For children not suspected of having a UTI by the GP, appropriate antibiotics were prescribed empirically at the index consultation in only two (7.1%) children, compared with six (85.7%) receiving appropriate empirical antibiotics if they were suspected of having UTI.

Overall, 6/35 (17.1%) children with a UTI had appropriate antibiotics prescribed at the initial consultation, a further two (5.7%) probably had appropriate antibiotics (sensitivities not given by laboratory), five (14.3%) had antibiotics prescribed to which the bacteria were resistant, and 22 (62.9%) were not prescribed antibiotics at the initial consultation.

More than half (54.2%) of the UTIs were caused by *E.coli* (Table 5.54). About a fifth (22.9%) were reported as 'Coliform', and a further fifth as other organisms. Among the 19 *E.coli* culture results, more than half (11; 57.9%) were resistant to at least one antibiotic. This included amoxicillin in every case. About a third of all *E.coli* cultured were resistant to two or more antibiotics (Table 5.54). Among the 16 non-*E.coli* UTIs, resistance to antibiotics seemed to be lower with only a quarter resistant to at least one antibiotic and of these, two (12.5% overall) were resistant to more than one antibiotic.

The laboratories were less likely to report antibiotic sensitivities for non-*E.coli* UTIs, with sensitivities not given in 6/16 (37.5%) of non-*E.coli* UTIs compared with 1/19 (5.3%) of *E.coli* UTIs.

Table 5.54: Summary of causative bacterial species and antibiotic sensitivities (n=35)

Name of bacteria	Number of UTI caused	Antibiotic sensitivities not given	Fully sensitive to antibiotics	Resistant to 1 antibiotic only	Resistant to ≥2 antibiotics
E.coli	19 (54.3%)	1 (5.3%)	7 (36.8%)	5 (26.3%)	6 (31.6%)
Coliform	8 (22.9%)	4 (50.0%)	1 (12.5%)	2 (25.0%)	1 (12.5%)
Enterococcus	3 (8.6%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
Coag-neg staphylococcus	3 (8.6%)	0 (0.0%)	3 (100%)	0 (0.0%)	0 (0.0%)
Citrobacter	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Staphylococcus	1 (2.9%)	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5.55 shows the association of causative organism, antibiotic prescription and clinical outcomes for children with UTI.

Table 5.55: Association of organism, antibiotic prescription and clinical outcomes at 6 months

	PID	Name of organism	Was prescribed antibiotic likely to treat UTI?	Surgery consultations	OOH or A&E contacts	No. courses oral antibiotics	Hospital referrals	Had or referred for USS
GP did suspect UTI	326	Coliform	Unclear	2	1	1	0	0
	1337	*E.coli*	Yes	3	2	4	1	1
	363	Coliform	No	1	0	1	0	0
	1823	*E.coli*	Yes	4	1	1	0	0
	1055	Coliform	Yes	0	0	0	0	0
	1154	*E.coli*	Yes	.	.	.	.	.
	1851	*E.coli*	Yes	.	.	.	.	.
GP did not suspect UTI	463	*E.coli*	No	6	0	2	0	0
	468	*E.coli*	No	1	0	1	0	0
	1938	*E.coli*	No	5	0	1	1	0
	1153	*Enterococcus*	No	7	1	3	0	0
	39	Coliform	No	6	0	3	0	0
	1085	*E.coli*	No	0	0	0	0	0
	461	*E.coli*	No	7	1	4	1	1
	472	*E.coli*	No	7	3	2	0	0
	396	*E.coli*	No	2	0	1	0	0
	1361	*E.coli*	No	7	4	2	1	1
	1832	*Citrobacter freundii*	No	4	0	4	1	0
	1342	*Coag neg staph*	No	3	4	1	0	0
	1368	*Enterococcus*	No	3	2	1	0	0
	1377	*E.coli*	No	5	2	4	1	0
	1383	*E.coli*	No	1	1	1	0	0
	2019	*Enterococcus cloacae*	No	.	.	.	.	.
	1029	Coliform	No	.	.	.	.	.
	1077	*Coag neg staph*	No	.	.	.	.	.
	156	Coliform	No	4	0	2	0	0
	158	Coliform	No	2	0	0	0	0
	408	*Staph**	No	5	0	0	0	0
	1685	Coliform	No	6	2	1	0	0
	2016	*E.coli*	No	1	0	0	0	0
	2063	*E.coli*	Unclear	0	1	0	0	0
	1382	*Coag neg staph*	Yes	.	.	.	.	.
	5002	*E.coli*	No	.	.	.	.	.
	3003	*E.coli*	No	1	0	1	0	0
	2057	*E.coli*	No	5	1	0	0	0

* *Staphylococcus*

There was only one acute hospital admission, one DMSA scan and no MCUG among all the children with UTI so these numbers were not presented in this table. I used a Mann-Whitney U-test to see whether there was a difference in outcomes between those in whom the GP suspected UTI and who generally received an appropriate antibiotic and those in whom the GP did not suspect a UTI and who generally did not receive an appropriate antibiotic. There was no significant difference in the median number of surgery consultations (P=0.33), OOH/A&E contacts (P=1.00); or courses of antibiotics between the two groups. The numbers in the follow up categories were small. More research is needed to explore this further.

Imaging of children with UTI and comparison with NICE guidelines

The NICE guidelines for imaging in children are divided into three age categories, which are slightly different from the three age categories used for diagnosis and symptoms. For imaging, the groups are aged: less than six months; six months or older but less than three years; and three years or older.

Table 5.56 shows the number of children who had been referred for or received ultrasound scans (USS), DMSA scans or MCUG scans in the six months following the index consultation.

Table 5.56: Imaging and referral during the six months following index consultation for children with UTI and a completed follow-up form (n=28)

Age range	Referred to hospital	Had or referred for USS		Had or referred for DMSA	
		Yes	No	Yes	No
<6 months	Yes	1	0	0	1
	No	0	3	0	3
≥6 months - <3 years	Yes	1	3	0	4
	No	0	14	0	14
≥3 years	Yes	1	0	1	0
	No	0	5	0	5
	Total	3	25	1	27

NICE states:

- "Infants and children with atypical UTI should have ultrasound of the urinary tract during the acute infection to identify structural abnormalities of the urinary tract such as obstruction."

- "For infants younger than 6 months with first-time UTI that responds well to treatment, ultrasound should be carried out within 6 weeks of the UTI."
- "For infants and children 6 months or older with first-time UTI that responds to treatment, routine ultrasound is not recommended unless the infant or child has atypical UTI."
- "Infants and children who have had a lower urinary tract infection should undergo ultrasound (within 6 weeks) only if they are younger than 6 months or have had recurrent infection."
- "A DMSA scan 4-6 months following the acute infection should be used to detect renal parenchymal defects."

Figures 5.10 – 5.13 are copied from the NICE guideline. Figure 5.10 defines 'atypical' and 'recurrent' UTI. Figures 5.11-5.13 show the recommendations from the NICE guidelines for imaging following UTI.

Figure 5.10: Definitions of atypical and recurrent UTI in NICE guideline

Atypical UTI includes:
- Seriously ill
- Poor urine flow
- Abdominal or bladder mass
- Raised creatinine
- Septicaemia
- Failure to respond to treatment with suitable antibiotics within 48 hours
- Infection with non-*E.coli* organisms

Recurrent UTI:
1) Two or more episodes of UTI with acute pyelonephritis/upper urinary tract infection or
2) One episode of UTI with acute pyelonephritis/upper urinary tract infection plus one or more episode of UTI with cystitis/lower urinary tract infection or
3) Three or more episodes of UTI with cystitis/lower urinary tract infection.

Figure 5.11: Recommended imaging schedule for infants younger than 6 months in NICE guideline

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	Yes
Ultrasound within 6 weeks	Yes[b]	No	No
DMSA 4-6 months	No	Yes	Yes
MCUG	No	Yes	Yes

[a] see figure 5.10 for definition
[b] if abnormal consider MCUG
[c] In an infant or child with a non-E.coli UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Figure 5.12: Recommended imaging schedule for infants and children 6 months or older but younger than 3 years in NICE guideline

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4-6 months	No	Yes	Yes
MCUG	No	No[b]	No[b]

[a] see figure 5.10 for definition
[b] While MCUG should not be performed routinely it should be considered if the following features are present:

- Dilatation on ultrasound
- Poor urine flow
- Non-*E.coli* UTI
- Family history of VUR

[c] In an infant or child with a non-*E.coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Figure 5.13: Recommended imaging schedule for children 3 years or older in NICE guideline

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[b c]	No
Ultrasound within 6 weeks	No	No	Yes[b]
DMSA 4-6 months	No	No	Yes
MCUG	No	No	No

[a] see figure 5.10 for definition
[b] Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition
[c] In an infant or child with a non-*E.coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

NICE recommends that all children under six months old should have an ultrasound within six weeks (in some children this should be during the acute infection). Only one of those under 6 months old had an USS (25.0%).

Those with atypical or recurrent UTIs are also advised to have a DMSA scan. It is difficult to see from the data I collected whether some of the criteria for atypical or recurrent UTI apply, so I have examined whether there was infection with non-*E.coli* organisms and whether there was a history of UTI previously. There were only two with a past history of UTI but I could not tell how many previous UTIs had occurred or whether it was an upper UTI or not. For this purpose I assumed that it was an upper UTI and so justified various imaging.

Table 5.57 shows the number of non-*E.coli* UTI and previous UTI (making the current episode a recurrent one) for different ages.

Table 5.57: Association of age with non-E.coli UTI and recurrence

Age range	Number with non-*E.coli* UTI	Number with history of UTI previously	Number who had USS	Number who had DMSA
<6 months	1	0	0/1	0/1
≥6 mths - <3 yrs	9	1 (1 of the 9 non-*E.coli* UTI)	0/9	0/9
≥3 years	2	1 (*E.coli* UTI)	0/3	0/3

Table 5.58: Comparison of imaging completed in study children within 6 months following UTI with NICE guideline recommendations

Age range	NICE guidelines recommend USS	Had or referred for USS	NICE guidelines recommend DMSA	Had or referred for DMSA	NICE guidelines recommend MCUG	Had or referred for MCUG
<6 months	4/4	1/4	1	0/1	1	0/1
≥6 mths - <3 yrs	9/18	0/9	9	0/9	0	0
≥3 years	3/6	0/3	1	0/1	0	0
Total	**16/28**	**1/16**	**11/28**	**0/11**	**1/28**	**0/1**

An ultrasound scan was indicated for all children less than six months old and half of the children in the older two age categories (Table 5.58). Only one (6.3%) of all the children in whom an USS was indicated, and none of the 11 in whom a DMSA scan was indicated, according to NICE guidelines, were reported as having had one or been referred for one in the six months following the index consultation. MCUG was only indicated in one child and was not done. ***This gives an overall guideline adherence for imaging of 1/28 (3.6%).***

In the youngest age category, one of the four children in whom an USS was indicated received one, and the one child in whom a DMSA scan was indicated did not receive it. There was one child in this age category who was referred to hospital during this period and so may have had investigations arranged by paediatrics that the surgeries were unaware of, but this was the same child who was reported as having an USS by the surgeries and was not the child with the non-*E.coli* UTIs in whom a DMSA scan was indicated.

In the middle age category (6 months – 3 years), nine of the 18 children were indicated for both USS and DMSA scans according to NICE. None of these children had either investigation, although one of the other children (in whom it was not apparently indicated according to NICE guidelines*) had an USS. Four children were referred to hospital in this age category. One of those referred had a non-*E.coli* UTI and was one of the nine in whom both USS and DMSA scans were indicated. If this child had received an USS and DMSA scan via the hospital referral, the surgery may not have known about that. The other three who were referred to hospital were not those in whom scanning was indicated. Therefore, for those in the middle category, assuming that the one child who was referred to hospital received scans, possibly 1/9 (11.1%) in whom both an USS and DMSA scan were indicated may have received them.

In the oldest age category, ultrasound and DMSA scans were indicated in three out of the six children. None of these children were reported by surgeries as receiving either of these tests, although another child in whom it was not apparently indicated* did receive both an USS and DMSA scan. This was also the one child in this age category who was also referred to hospital.

* NB these children may have fulfilled some of the other criteria for atypical UTI e.g. septicaemia or failure to respond to antibiotics within 48 hours and so investigations may have been indicated.

Chapter 6: Discussion

Summary of Methods and Results

Summary of what was done

I completed a systematic review of the literature relevant to estimating prevalence rates in acutely ill children with systematic urine sampling in primary care settings (GP and A+E; chapter 2). I found that it was not clear what the prevalence rate of UTI was for unselected ill children presenting in UK primary care and concluded that a prospective study was warranted to determine prevalence of UTI in the UK.

A pilot study, in four GP practices in South Wales with 99 children, showed that it was feasible to recruit and obtain urine samples from acutely ill children in general practices (chapter 3).[150]

I undertook a prospective study of 597 children, with systematic urine sampling, of children aged less than five years who presented to their GP with an acute illness of less than 28 days duration to provide an estimate of the prevalence of UTI. Thirteen GP practices and five NHS laboratories across Wales participated between March 2008 and July 2010. Children were excluded if they were on immunosuppressant treatment or long-term antibiotic treatment or had previously taken part in the study. I aimed to recruit 1600 children to give a sample size of 1100 with urine samples, allowing for some (30%) not providing urine samples. The sample size calculation was based on a predicted (estimated) prevalence of 3% with a 95% confidence interval of +/- 1%.

Presenting symptoms, signs, risk factors, examination findings, working diagnosis and treatment were recorded on the CRF at the index consultation. A urine sample was requested from all children and obtained before leaving the surgery where possible. The urine sample was tested with a dipstick (where possible) and then sent to the local NHS laboratory using routine processes.

A positive culture was defined as pure or predominant bacterial growth of $>10^5$ cfu/ml on culture. All other results were considered negative for the main analyses. Additional sensitivity analyses defined a borderline culture as 10^4-10^5 cfu/ml of a single organism (in

laboratories which recorded growth at this level) or $>10^5$ cfu/ml of two organisms. Urines with heavy mixed growths ($>10^5$ cfu/ml of more than two organisms) were considered contaminated.

A telephone follow-up questionnaire was completed at 14 days after the index consultation, for children with a positive or borderline culture result. A six month follow up questionnaire was sent to surgeries for all children who had provided a urine sample at the index consultation.

Practices were asked to keep recruitment logs for eligible children who consulted, and record numbers of children invited and those consenting to participate. A check was made to see whether age and gender profiles were consistent with the practice population.

The main analysis was limited to children from whom a urine sample had been provided within 48 hours of the index consultation (and where the laboratory had been able to analyse the specimen). I described the association of symptoms, signs and risk factors with UTI. I used the univariable analyses as a screening tool for inclusion of symptoms and signs (with a p-value of <0.1) into a multivariable logistic regression model.

I calculated the probability of UTI for children in my study based on symptoms and signs using the model. I used the probabilities from the model to propose a urine sampling strategy for use by GPs. I compared my proposed sampling strategy with the sampling strategy advised in the NICE guideline and with sampling based on GP suspicion of UTI.[1]

Summary of study population

A total of 1003 eligible children were recruited from 13 general practices. Recruitment rate varied between practices from 1.5 per month to 11.7 per month. Four practices were not able to complete recruitment logs. The nine practices that did complete recruitment logs listed 63 eligible children who were approached but not recruited. Median age of recruited children was 2.3 (IQR 1.0-3.5) compared with non-recruited children with a median age of 1.6 years (IQR 1.0-3.1).

Urine samples were obtained in 709 (70.7%), but leaked in 23 (3.2%) cases. Intact urine samples were received by laboratories within 48 hours of the index consultation in 597 cases (59.5%) and only these were included in the main analysis.

Urine samples were obtained before the child left the surgery for 318 (53.2%) of the children included in the analysis. It was much less likely that the urine sample was received within 48 hours of the index consultation if the sample was obtained after leaving the surgery ($p<0.01$). Antibiotics were prescribed in 31.1% (99/318) of children who provided urine samples prior to leaving the surgery and in 25.1% (70/279) of those who did not.

A comparison of children included in the main analysis with those who did not provide a urine sample within 48 hours of the index consultation, found that children not included were younger (median age 1.6 years compared with 2.3 years in those included; $p<0.01$). There was a higher proportion suspected of UTI by GPs in those included in the main analysis than in those not included.

Summary of main findings

The prevalence of UTI among 597 systematically sampled acutely ill children less than five years old presenting in primary care was 5.9% with 95% confidence intervals of between 4.3% and 8.0%. The prevalence of UTI was higher in younger children, with children under three years old having a prevalence of 7.3% (95% CI 5.1-10.4%) compared with children aged three years or older having a prevalence of 3.2% (95% CI 1.6-6.5%; $p=0.04$).

There was no significant difference in the prevalence of UTI between boys and girls younger than three years old, but UTI was more common in girls than boys in children aged three years or older, with a prevalence of 7.1% (95% CI 3.5-14%) in girls and 0.0 (95% CI 0-3.2%) in boys ($p<0.01$).

Prevalence did not appear to vary with deprivation, month of the year or GP surgery. There was a suggestion of some variation in prevalence depending on which laboratory processed the sample, however numbers were too small to determine whether this was significant.

In 431 (72.2%) the method of urine sampling was given. Nappy pads were used in the majority of children less than three years old (100.0% in those aged <3 months; 74.3% in

those aged ≥ 3 months to <3 years). Clean catch collection was used in all children ≥ 3 years old. There was no statistically significant difference in the prevalence of UTI between nappy pad and clean catch samples (p=0.19).

The definition of UTI used was a pure or predominant growth of bacteria of $>10^5$ cfu/ml on culture of urine. In addition to the 5.9% which fitted this criterion, a further 1.8% had a pure or predominant growth of bacteria of between 10^4 and 10^5 cfu/ml and 1.0% had predominant growths of $>10^5$ cfu/ml of two different bacteria. Mixed growths were reported in 48.4% of samples. A heavy mixed growth of $>10^5$cfu/ml was reported in 34.8%. Some laboratories commented that mixed growth was likely to represent contamination. Heavy mixed growths were more common in nappy pad samples (61.7%) compared with clean catch samples (13.2%; p>0.01).

Urine samples were not cultured in 40 (6.7%) cases.

The most common bacteria cultured were *E.coli*. These were responsible for 54.2% of UTIs. An additional 22.9% were reported as Coliforms. More than half of the E.coli (57.9%) and 37.5% of the Coliform were resistant to one or more antibiotic.

Antibiotics were prescribed at the index consultation (prior to urine culture results) in 37.1% of children subsequently found to have a UTI and in 27.8% of those who did not have UTI. Antibiotics were more likely to be prescribed if the GP suspected UTI (p<0.01). Appropriate (according to the eventual sensitivities) antibiotics were prescribed at the index consultations in 6/7 of those who had UTI and who were suspected of having UTI by the GP. In the 28 with UTI who were not suspected of UTI, only one had an appropriate antibiotic prescribed at the index consultation.

A multivariable logistic regression model identified age range, pain or crying on passing urine and increased urinary frequency (or frequency of wet nappies) as being associated with UTI. Neither a history of fever nor the absence of an alternative site of infection was significantly associated with UTI.

Using the multivariable model, the probability of UTI in children less than three years old, irrespective of presenting symptoms and signs, was >5%. In children aged three to five years,

with neither pain on passing urine nor increased urinary frequency, the probability of UTI was 2%.

Therefore a possible strategy of sampling urine in all children under the age of five years old except those three years or older without urinary symptoms was considered. This proposed strategy was compared with the urine sampling strategy in the NICE guidelines and with urine sampling according to GP suspicion of UTI. I estimated that the proposed strategy would identify 97% of UTIs and would only miss 3% of UTIs, compared with 51% which would be missed if NICE guidelines were followed and 80% if sampling was based on GP suspicion alone. However, this would involve sampling twice as many than is currently recommended by NICE guidelines and ten times more than would be sampled based on GP suspicion alone.

Of the children diagnosed with UTI and with two week follow-up data (n=18), nine (50%) had an illness which lasted more than two weeks. None had been admitted to hospital.

Among the children with six month follow up data (n=28 with UTI; n=487 without UTI), there was no difference in the number of re-consultations with GPs, number of acute admissions, number of out of hours or A&E contacts or number of hospital referrals between those with and those without UTI in the six months following the index consultation. Children with UTI were treated with more courses of antibiotics than those without, and were nearly twice as likely to have received two or more courses of antibiotics in the subsequent six months (p=0.02).

Of the children diagnosed with UTI and with six month follow-up data (n=28), three children had been referred for or had an USS and one child had received a DMSA scan. No children had been referred for or received a MCUG. Comparing the investigations which children received with those advised by the current NICE guidelines, showed that only 1/16 recommended children received an USS and none of the 13 recommended received a DMSA scan. The one child in whom a MCUG was indicated did not receive one. Two children received an USS and one child a DMSA scan when this did not seem to be indicated by NICE guidelines. The overall guideline adherence for imaging was 1/28 (3.6%).

Strengths

Literature review

A literature review and systematic review of prevalence determined the importance of the research question and the need for a large prospective prevalence study, with systematic urine sampling, in UK general practice.

Pilot study

The pilot study showed that it was feasible to recruit young children from general practices and obtain urine samples.[150] It helped to secure funding to conduct the large study. Feedback from pilot study participants informed the method and CRF development for the main study.

Prospective study with systematic urine sampling

This was a prospective study with the estimated prevalence of UTI based on the urine samples from nearly 600 children recruited from GP surgeries in Wales, UK. This is the largest published study of this kind in UK general practice. It is important that the study was conducted in the UK, as the results of studies from other countries may not be generalisable to general practice in the UK due to differences in health care systems, consulting behaviour and socio-demographics.

The results of related studies conducted in *A&E departments* (see chapter 2), despite using systematic sampling methods, may not be generalisable to acutely ill children presenting in *general practice*.[48 60 63 65-68 70 71 73 83 100-103 151 152 154] Although it is a primary care service, children presenting to A&E departments are likely to be different to those presenting to their General Practitioner (GP). This may be partly dependent on the country of origin of the study. Children presenting to A&E may be more seriously ill or they may have been taken to A&E due to increased parental concern. GPs interested in the probability that a child presenting with an acute illness, *in their surgery,* has a UTI will be more convinced by the prevalence of UTI among children presenting in a similar way to other GP practices, rather than data from children who present at A&E.

This was a prospective study. All of the symptoms, signs, risk factors, examination findings, working diagnosis and treatments were recorded prior to the determination of UTI status. This means that any association of these variables with UTI status could not be explained by

the influence of practice or research nurses or doctors knowing the case status and introducing biased associations (reporting bias).

Systematic urine sampling was one of the greatest strengths, and an important aspect of the design, of this study. The prevalence of UTI could not be determined accurately in a group of children in whom it was known that cases are easily missed[43] without systematically sampling urine samples from all acutely ill consulting children. I achieved a 70% urine sample retrieval rate, with a resultant 597 urine samples finally available for the analysis. Although I had hoped for a higher retrieval rate, and ideally wanted all of the children to provide urine samples, obtaining 70% urine retrieval rate in this population and setting is a strength of this study. The key aspect of my study was that a sample *was requested from all children*, not just in children in whom the clinician suspected UTI. Although it is still possible that clinicians and parents were more or less enthusiastic in encouraging urine samples from some children, I tried to limit this in the study. Practice or research nurses requested a urine sample in most cases even before the child had been seen by the clinician, and everyone participating in the study was aware of the importance of obtaining urine from all children irrespective of presenting symptoms or what they thought the likely diagnosis was. Surgeries were reimbursed with less money if they recruited a child without a urine sample. This method reduces the chance of selection bias which has been present in many of the studies reporting UTI prevalence rates, as urine samples in other studies are often only requested if the clinician suspects UTI may be present.

My study used usual GP and NHS processes for collection, transport, analysis and reporting of urine samples. This means that my results are more applicable to everyday general practice. The prevalence rate in my study should reflect the prevalence rates which other GPs in the UK will get if they were to systematically send urine samples on their acutely ill consulting children to their local NHS laboratory. Therefore the prevalence rate in my study should be a good estimate for the probability of UTI in a consulting ill child in their routine practice. Even with the inherent problems in the current system (e.g. delay in transport to laboratory) and with the diagnosis of UTI (imperfect gold standard), conducting a study in this pragmatic way means that it can be immediately incorporated into these systems and will be useful in everyday (imperfect) practice.

Broad inclusion criteria

Most published studies use highly selected groups of children. Often children are only recruited if they have a high fever, commonly >38°C. [48 60 63 65-68 70 71 73 83 100-103 151 152 154] Other studies have shown that UTI can be present without fever and can still be associated with renal scarring.[81] In addition, there are problems with basing study inclusion on fever as the definition of fever is difficult,[80] there is wide variation in the methods used and the accuracy of these, and children may have had anti-pyretics or be at different stages in the illness perhaps with different associated temperatures. With the evidence that many UTIs were being missed in primary care,[43] I wanted to be sure that I did not exclude children purely on the basis of a presenting symptom or sign. Many published studies also included only children with narrow age ranges, with most studies using systematic sampling only in very young children. The majority of studies included in the systematic review of Shaikh et al,[145] and those included in my systematic review in chapter two, are of children less than three months old.[48 61 63 65-67 70 71 100-103 151-153]

I wanted to determine the prevalence in a typical ill child presenting in the surgery and also in the youngest children where the association with long-term complications is strongest.[12] Another exclusion criterion in other studies is of children with an alternative source of fever or other diagnosis. However, there is evidence that UTI can occur in children with (or thought to have) other diagnoses.[48] I wanted to include all these children irrespective of the working diagnosis of the clinician.

Analysis limited to urine samples processed within 2 days of the index consultation

I only included urine samples which were received by laboratories within 2 days of the index consultation for the main analysis. This was to make sure that the urine sample related to the presenting symptoms and signs of the acute illness with which the child consulted. This was an arbitrary cut off point on which I decided following discussion with my supervisors. The more time which passes between the index consultation and collection of the urine sample, the more likely that any UTI present may have been cleared or a new illness developed, or antibiotics been taken and the urine sample may not accurately reflect the illness at the index consultation.

Determination of prevalence and confidence intervals

I determined the prevalence of UTI in this population with fairly narrow confidence intervals. The prevalence was substantially higher than I had expected and is an important finding. The lower 95% confidence interval value was 4.3% which is likely to be clinically significant as GPs will encounter it commonly in routine practice. We can be confident (at least a 95% chance) that the true population prevalence of UTI in children under the age of five presenting in UK general practice with an acute illness is at least 4.3%. The clinically significant question is: 'is the prevalence (pre-test probability) high enough to justify urine samples in all acutely ill children?' With the lowest estimate for the 95% confidence interval being 4.3%, it is likely that clinicians will consider changing their urine sampling behaviour.[40]

Presenting symptoms & signs for children with UTIs including those previously un-described

I have described the presenting symptoms and signs for a group of children with UTI which includes children who would not have been detected in previous studies without systematic urine sampling. Children with UTI diagnosed in this way from general practice have not been described before. It may be that the UTIs in these children are different from the UTIs which are diagnosed when urine samples are only sent when UTI is suspected by clinicians. Although my study was not powered to accurately determine the predictive value of symptoms, signs and risk factors, it provides unique descriptive information about UTI diagnosed through attempted systematic sampling.

Data gathered on those not recruited & not included in analysis

Gathering data on those not recruited and those not analysed has allowed me to assess evidence of selection bias.

There was a difference in age between those who were included in the main analysis and those who were not, with younger children less likely to provide a urine sample within 48 hours ($p<0.01$). Children not included in the main analysis were approximately seven months younger than those included (median age 1.6 vs. 2.3). There was no difference in gender between these two groups. There was a higher level of GP suspicion of UTI among those included in the main analysis compared to those not included (OR 2.2; $p=0.01$). This could be due to GPs encouraging urine samples more in children in whom they suspected UTI or

perhaps parents were more inclined to obtain the urine sample if they considered their child could have a UTI (perhaps if they had urinary symptoms). It could also relate to the fact that younger children were less likely to be in the main analysis and they are more likely to have non-specific symptoms. There was an association between GP suspicion of UTI and actual UTI (GPs suspected UTI in 20% of those with UTI compared to 6% in those without; $p<0.01$). If GPs encouraged parents to obtain urine samples more actively when they suspected UTI, and given that GP suspicion is associated with an increased likelihood of UTI, this may indicate some selection bias leading to a slight overestimation of the prevalence.

Weaknesses

Sample size

I did not recruit the numbers for which I had aimed following my sample size calculation and so the confidence intervals were wider (+/- 2%) around my estimate than I had planned. The sample size was also not large enough to accurately determine predictive values for presenting symptoms and signs. This resulted in large confidence intervals for the odds ratios and probabilities in the multivariable model.

The target of 1100 children with urine samples was ambitious for a modestly funded study in general practice involving children. A previous study of febrile children in the UK had struggled to recruit (target sample size 747; recruited 156).[160] The pilot study showed that it was feasible to recruit acutely ill children from primary care.[150] Several factors may have hindered recruitment for the main study. There were two structural changes which occurred during the approval and recruitment of practices. These were the changes to the R&D and ethics approval processes for primary care in April 2009 with the development of SPARC (Streamlined NHS Permissions Approach to Research – Cymru), and the restructuring of the NHS in Wales moving from 22 local health boards and 7 hospital trusts to just 7 local health boards (covering primary and secondary care) in October 2009. These two changes caused substantial delays in the approval of new practices to recruit for the study. Many practices withdrew agreement to participate and several that had agreed and finally received approval were only able to recruit for a short time.

In addition, the swine flu pandemic of 2009 (affecting UK from April –Dec 2009) may have affected recruitment as practices were busy dealing with this pressing clinical and public

health problem and ill children (and adults) thought to have flu were advised not to come to surgeries.

Obtaining urine samples from children in general practice is difficult and presumably some of the problems which I encountered with recruitment and urine retrieval were due to this. The other problem was that the children I wanted surgeries to recruit were the acutely ill children who were often consulting as emergencies, being squeezed in as extras in already busy clinics.

Multiple significance testing

I tested many potential predictive variables and this increased the likelihood that some would be statistically significant purely by chance. The p-values and associations found with the univariable analyses need to be interpreted in this context, and were conducted as a screening test to see which variables to enter in the multivariable logistic regression.

Selection bias

Practices

Ideally, I would have taken a random sample of GP practices from Wales. Following my experience with the pilot study, I attempted to recruit practices in a systematic way, and sent out study information to all practices in the Cardiff and Vale area that had two or more GP partners or two or more practice nurses. I felt that the best chance of recruiting sequential children would be in practices large enough to have the space and resources to have a nurse recruiting for the study with protected time and space to facilitate this. Unfortunately there were not enough practices interested among this group and so all the practices in the Cardiff and Vale area were invited to participate and practices in other areas were also targeted.

Selection bias could have occurred if the practices which participated in the study were systematically different to the practices which did not participate in terms of their prevalence of UTI, consulting behaviour of ill children, or recruitment of children into the study.

If a practice had a policy of encouraging ill children not to attend the surgery or assessing more children over the telephone this could affect the prevalence of UTI by reducing the denominator (acutely ill consulting children). If a practice was in an area with high levels of

consulting for minor illness, the denominator may be much larger. This would not result in bias if the prevalence of UTI was similar in those consulting and those not consulting.

Practices agreeing to take part in the study were more likely to be bigger practices (bigger practices were initially targeted) with some flexible nursing capacity which could be used for recruitment. Practices which were already research active and those which had already taken part in the pilot study were more likely to agree. Practices agreeing to participate may have had GPs or nurses who had an interest in UTI.

The practices in the study were from a range of affluent and deprived areas. They had larger list sizes than the average in Wales (mean 10,353 compared with 6,242) and higher than the average number of children under five years old registered (7.1% compared with 5.5%).
I did not find evidence of significant variation in prevalence between practices. It is unlikely that selection of practices resulted in biased prevalence results.

Children

Not all the children presenting in practices were recruited and not all recruited children provided a urine sample. This could have resulted in bias if there was a systematic non-recruitment or systematic non-provision of urine samples in children more or less likely to have a UTI. I requested that practices recruit all eligible children and ask all children to provide a urine sample irrespective of whether they suspected that they may have a UTI. Ideally practices would recruit *every* eligible child, but this is not possible in reality and I knew from my experience with the pilot study that they would not do this.

Many practices chose to only recruit on certain days or during certain sessions (e.g. mornings). I asked practices not to recruit on a Friday afternoon due to the problems with getting urine samples to laboratories. Not recruiting on certain days is unlikely to have resulted in bias as time of recruitment is unlikely to be linked to UTI prevalence.

Selection bias would be a problem if nurses or GPs were selecting children for recruitment into the study based on suspicion of UTI. There were several ways in which I tried to limit this from happening. Firstly, I emphasised the importance of recruiting all children irrespective of suspicion of UTI or not. Secondly, practices were financially reimbursed for all children whom they recruited irrespective of UTI status, and were reimbursed a higher

amount if a urine sample was obtained. This reduced the possibility of there being some systematic selection to the study. Also, the nurses and clinicians recruiting, consenting and treating the children were unaware of UTI status as this was a prospective study. Given that presenting features and clinician suspicion of UTI are poor predictors of actual UTI it seems unlikely that there was substantial selection bias in this way. I also asked practices to keep recruitment logs of those approached but not recruited to see if there were any differences between recruited and non-recruited children which may suggest selection bias.

It is likely that the more seriously ill children were not recruited into my study. I asked practices to recruit children even if they were being admitted to hospital but, in reality, this would have been difficult, and probably inappropriate, for practices to obtain informed consent for this study, record data and attempt to obtain a urine sample when the child was seriously ill. I did ask practices simply to consent children and record personal data and not to collect the majority of CRF data or a urine sample (assuming it would be taken in hospital) but there were no patients in my study who were admitted on the same day as the index consultation. This is likely to have resulted in selection bias and probably an under-estimation of the prevalence of UTI. However, in practice, a GP urine sampling strategy is unlikely to apply to seriously ill children who are being admitted into hospital in any case.

Although all children were asked to provide a urine sample, and practices were financially incentivised to obtain a urine sample in all children, there was only a 70% urine retrieval rate, and this dropped to 60% when only those providing urine samples within 48 hours were analysed. Even if clinicians were not selectively encouraging urine samples from certain children, it is likely that those who provided a urine sample within 48 hours were different from those who did not, and this could be associated with UTI prevalence. It seems likely that more seriously ill children may have been more difficult to obtain urine samples from, perhaps if the child was more dehydrated or agitated or taken to hospital and parents less focused on a research study. On the other hand, if a child was more ill the parents, GPs and nurses may have shown a greater degree of commitment to obtaining a urine sample. If a child was less ill or had no urinary symptoms, an obvious infection elsewhere (e.g. ear infection) or recovered from their illness very quickly, parents may not have seen the point or tried so hard to obtain a urine sample. Children with UTI may have avoided passing urine due to pain, making obtaining the urine sample more difficult.

Patients living further away from the surgery may have been less inclined to return the urine sample if they were unable to provide the sample in the surgery. This may have resulted in fewer samples from more deprived or rural areas.

Overall, I think it is mostly likely that these factors resulted in my sample of children under-representing the most ill children and may have resulted in a slight under-estimation of the prevalence of UTI.

Attrition bias

Children in main analysis older than those not included, and recruited children older than non-recruited

The recruitment logs showed that children who were recruited were older than children who were not (median age 1.9 years vs. 1.6 years). Of the children recruited, children who provided urine samples within 48 hours and who were included in the main analysis, were older than those who did not (median age 2.3 years vs. 1.6 years). This may reflect the difficulties of obtaining urine samples in younger children. I found that younger children had a higher prevalence of UTI and as they were less well represented in my analysis, this may indicate that my prevalence of 5.9% is an underestimation of the true population prevalence.

Loss to follow up was not a major problem for the main outcome or for the multivariable model. However, the outcomes from the 14 day telephone interview and the 6 month questionnaire were subject to loss to follow-up which can be a source of (attrition) bias. The biggest problem was with the telephone follow up which was only completed on 57% of targeted (positive or borderline culture result) children. In 70% of cases where telephone follow up was not completed, this was due to the results not being available in time. Due to this, and the overall numbers very small, there is limited analysis on the telephone follow up data. Six month follow up forms were completed in 99% of those in whom they were requested. Follow up forms were not requested in 78 (13%) of those who should have been sent them (follow up forms were not requested from children who had not provided a urine sample) due to the urine results not being available until after the follow-up data collection period.

Other sources of bias

Misallocation

Misallocation is an important issue. The problem of false positive and false negative results is significant and impossible to quantify due to the lack of a reliable gold standard. This problem is exacerbated in a primary care study in children where samples are more likely to be contaminated and there are likely to be delays in transport to the laboratory. Misallocation may also have occurred if the child had asymptomatic bacteriuria and a coincidental acute illness. The issue is whether misallocations are likely to have been random (in which case the true associations may simply have been diluted) or associated in some way with UTI or risk factors, in which case it would result in bias.

Variation in laboratory procedures may have resulted in misallocation. It would have been ideal to have had all the urine samples analysed in one laboratory, with high quality procedures and standardised SOPs, but this was not possible for my study. I found that there was variation between laboratories in procedures for storage, analysis and reporting of urine cultures which may have affected my prevalence estimate.

Contamination

Contamination was more common in nappy pad urine samples. The nappy pads were used in the younger children and the prevalence of UTI was highest in the younger children. There was no statistically significant difference in the prevalence of UTI between nappy pad and clean catch samples which implies that although contamination (and presumably misallocation) was more common in nappy pad samples, this was not associated with the prevalence of UTI. However, the numbers may have been too small to detect a statistically significant difference (type II error).

Another source of misallocation could be due to antibiotics prescribed at the index consultation and taken before the urine sample was provided. Only including urine samples obtained within 48 hours of the index consultation reduces the risk of this, and GPs may have advised parents not to start antibiotics until the sample had been obtained. However, it is possible that some children with UTIs were misallocated as a result of this. Antibiotics were prescribed in 31% of children who provided a urine sample prior to leaving the surgery and in 25% of children in whom a urine sample was obtained after they left the surgery (but within 48 hours). Of those who did not provide a urine sample before leaving the surgery, there was

no difference in the prevalence of UTI according to whether or not antibiotics were prescribed (p=0.33).

Summary of potential sources of bias

Table 6.1 summarises the potential sources of bias which I have identified and the likely effect of these on the prevalence of UTI in my study.

Table 6.1: Summary of potential sources of bias and possible effect on prevalence of UTI

Source of bias		**Likely effect on UTI prevalence**
Selection bias (practices)		None
Selection bias (children)	Younger children less likely to be included (included children older than not included)	Underestimation
	Seriously ill children less likely to be included (no included children admitted to hospital; less likely to participate in research if very ill)	Underestimation
	Dehydrated children less likely to be included (less likely to produce urine sample within 48 hours)	Underestimation
	Parents/clinicians did not think UTI likely (possibly less commitment to obtaining urine sample)	Overestimation
	Children with UTI may have had pain on passing urine and less likely to produce a urine sample	Underestimation
	Parents living further away from the surgery may have been less likely to return urine samples	None
Misallocation	Contaminated and nappy pad samples are more likely to result in misallocation. This could result in false positive results or false negative results.	Unclear
	Antibiotics taken prior to urine sample being provided could cause false negative results	Underestimation

Generalisability of findings

My study was conducted in GP practices in Wales. The primary care system in Wales is similar to the rest of the UK. It may not be the same as other countries in Europe or worldwide. All healthcare systems will have a similar problem of acutely ill children presenting to doctors, but the underlying prevalence of UTI in the population of acutely ill children may vary. The consulting behaviour of ill children may also vary between countries. This may mean that the estimate of prevalence of UTI which I have found in my study is not directly generalisable to other countries. Other studies have found variation in UTI

prevalence by ethnicity and circumcision status and I did not have sufficient numbers to explore these associations in my study.

No children were recruited in my study out of normal surgery hours (i.e. in the evening or at the weekend). It is possible that children presenting in the evening or at the weekend are different from those consulting during normal hours, perhaps with more serious illness, and possibly with a different risk of UTI. This will not result in bias in my study, it simply means that my findings may not be generalisable to this other group of children. This group of children is well represented in other studies conducted in A+E departments.

There is evidence that UTI prevalence may vary with ethnicity.[48 68 76 77 145] I did not collect data on ethnicity in my study. This may need to be taken into consideration when extrapolating my findings to areas of differing ethnic makeup.

Other considerations

The two symptoms included in the multivariable logistic regression model (pain or crying on passing urine and increased frequency of passing urine or wet nappies) may have been difficult to determine in the youngest group of children and numbers were particularly small in this group. However, this may not impact on clinical management as the prevalence in this group was high irrespective of symptoms, and a urine sample indicated in all of them.

Statistics

Multi-level sampling

I assessed the impact of the multilevel (two level) sampling, using the intraclass correlation coefficient (ICC). This was a way of measuring the impact of taking a sample of surgeries and then a sample of children from the surgeries. I found that the variation between practices accounted for only a small amount (5.6%) of the overall variability in prevalence of UTI.

Logistic regression

Logistic regression assumes independence of errors. This means that cases of data should not be related in any way. This is one of the reasons for including children into the study only once. Logistic regression also assumes that the different prediction variables are not too highly correlated with each other. I assessed the correlation of the variables which I entered

into my model with each other. There was some correlation between dysuria and frequency and age. Therefore, I included the interaction terms as well as the separate variables in the forward stepwise logistic regression model but they were excluded by the analysis and only the individual variables were included in the final model.

Validity

Internal validity and model fit

I used all the available data to develop the model and assessed the performance of the model on the same data.

I found that the model was significantly better at predicting UTI than the constant only model ($p<0.01$). However, the model does not explain much of the variation in the data. A Nagelkerke R^2 of .08 indicates that the model predicts only 8% of the variation in the data, with 92% unaccounted for. This may be because my sample size was not large enough to give enough power to detect associations with enough certainty and I may not have included the (truly) correct variables in the model. It may be that it is not possible to highly predict UTI in young children from symptoms and signs.

External validity

External validity is the generalisability of the model to other similar populations. It is essential to confirm external validity for any prediction model. I have not been able to assess the external validity of my model but hope to be able to assess this, and how my proposed sampling strategy performs in another similar dataset as part of future work.[176]

From prediction model to clinical decision making

The prediction model which I derived was associated with probabilities with very large confidence intervals.

When I considered possible sampling strategies in view of the logistic regression model, I was acutely aware of the large confidence intervals for probabilities particularly when considering the effect of the two symptom variables after the age categorisation. If just the age was considered, the lower confidence interval for the probability of UTI for both children <3 months and children <3 years was >4%. This means that there is reasonable certainty that the probability of UTI in a child less than 3 years old is at least 4% irrespective of presenting

symptoms. For children aged 3-5 years, the 95% confidence interval for the probability of UTI was from 1.6-6.5%, implying that it may not be as necessary to sample urine in all of these children. Looking at the probabilities of UTI with associated confidence intervals for the addition of the two symptom variables in the logistic regression model (dysuria and frequency) the probability was high if both symptoms were present (17%; 95%CI 5.4-74.7%); moderately high if either of the symptoms was present (6-7%), but much lower if neither were present with fairly narrow confidence intervals (2%; 95% CI 1.0-5.0%). If neither dysuria nor frequency are present in a 3-5 year old child, we can be reasonably certain that the probability of UTI is <5%.

My proposed sampling strategy (based on the logistic regression model) gives a sensitivity of 97.1% and specificity of 32.4% for UTI.

A major implication of my proposed sampling strategy is that it would require a large increase in urine sampling which is likely to be costly, time consuming and the majority of samples will be negative. However, it does require less urine sampling than a strategy of sampling urine from all acutely ill children, which is also a potential strategy given that the overall prevalence of UTI is probably sufficiently high to consider this.[40]

If my sample size had been larger with more power to detect the predictive value of symptoms with greater accuracy (and narrower confidence intervals) I may have been able to propose a more specific decision rule.

Choice of predictive values

I have chosen to present sensitivity and specificity when describing the predictive value of symptoms, signs or when describing my model. Other features could have been presented, for example positive/negative predictive values and positive/negative likelihood ratios. All of these values can be calculated from the data presented. I felt sensitivity was the most important feature to present as this is the best measure of how many children with UTI would be missed with the various models.[177]

Comparison with existing literature and clinical implications

In this section, each paragraph from the summary of findings (at the beginning of this chapter) will be discussed in detail.

Prevalence of UTI

The prevalence of UTI among 597 systematically sampled acutely ill children less than five years old presenting in primary care was 5.9% with 95% confidence intervals of between 4.3% and 8.0%. The prevalence of UTI was higher in younger children, with children less than three years old having a prevalence of 7.3% (95% CI 5.1-10.4%) compared with children aged three years or older having a prevalence of 3.2% (95% CI 1.6-6.5%; p=0.04).

The prevalence of UTI was higher than I had expected based on earlier primary care studies.[1 43 60 68 178] It is also higher than the prevalence I found in the pilot study (chapter 3).[150]

It is slightly lower than the pooled prevalence of 7% which was found in a systematic review and meta-analysis of prevalence of UTI in children.[145] However, as the studies included in this systematic review generally had very narrow inclusion criteria (e.g. aged under 3 months old and with a fever >38^{o}C) and were not necessarily systematically sampled, I had expected the prevalence in my study to be much lower than this. The prevalence I found in the younger children (less than three years old; 7.3%) was very similar to this pooled prevalence.

The comparison of the prevalence which I have found should be compared with other studies which have systematically sampled urine from children (rather than sampled according to clinician suspicion), and with studies which have a presenting population of unselected children (i.e. primary care settings including GP surgeries, out of hours and A&E departments rather than secondary care settings where children have already been selected for admission or follow-up by other clinicians). In chapter 2, I presented a systematic review of published studies which described the prevalence of UTI in acutely ill children less than five years old, presenting in primary care.

The pooled prevalence of these studies was 7% for those aged less than 3 months old (n=15) and 8% for those up to 5 years old (n=6). These studies were all based in primary care and had systematically sampled urine. However, most of the studies (19/21) were based in

paediatric emergency departments rather than GP surgeries, which may have represented a more seriously ill population of children; 17/21 studies were based in the USA; and 19/21 included children only if they had a fever of at least 38^{o}C. In addition, there was a high degree of heterogeneity between studies, particularly between the six studies for the older children.

There are several possible explanations for the difference in findings between mine and other studies. This is the first large study in UK primary care which systematically samples urine from acutely ill children and is likely to give a more accurate estimate of the true prevalence of UTI in the population of children under the age of five with acute illness than other studies which have either had clinician suspicion-led urine sampling or have been conducted systematically in secondary care or in only highly selected children.

I did not exclude children if they did not have a fever or if they had alternative sources of infection, which could have resulted in my study having a lower UTI prevalence than other studies. The UK population has low levels of circumcision and higher proportions of white children, compared with the USA where most previous studies have been conducted.[157 179] The circumcision rate among boys in my study was only 2.8% which is similar to the UK average whereas it is approximately 80% in USA.[158] Not being circumcised and being white have both been found to be associated with a higher risk of UTI in other studies.[48 63 68 76 77 102 145] This may partly explain why my study prevalence is higher than other published studies.

The children who were included in my analysis were older than the children not included having not provided a urine sample within 48 hours. Obtaining urine samples from the youngest children is difficult. Of the children who were included in my study, the prevalence was highest in the youngest children. This has also been found in other studies. This may have resulted in the prevalence in my study being lower than the true value due to fewer of the youngest children being included in the analysis.

None of the children in my study were admitted to hospital and none of them were scored as being seriously ill by parents or GPs on the 5 point illness severity score. Although I found no association between illness score (by parents or GPs) and UTI, the under-representation of the most ill children in my study may have resulted in an under-estimation of the true prevalence of UTI in acutely ill children.

Gender and age

There was no difference in the prevalence of UTI between boys and girls younger than three years old, but UTI was more common in girls than boys in children aged three years or older, with a prevalence of 7.1% (95% CI 3.5-14%) in girls and 0 (95% CI 0-3.2%) in boys (p<0.01).

Other studies have found that the prevalence of UTI is higher in boys in the youngest children, until about 3-6 months old; after this, UTI is more common in girls.[1] I also found that UTI was more common in girls in the older children (aged 3 years or older). In children under three years old I found there was no difference in UTI prevalence between boys and girls. It may be that my numbers were not large enough to detect gender differences in the youngest children. It may be that UTI is equally prevalent in young boys and girls but that previous studies have disproportionately detected UTI in boys, perhaps if it is associated with more severe illness or structural abnormalities. Some studies have found that among children with UTI, boys have a higher proportion of pyelonephritis and serious bacteraemic UTI than girls.[58 180]

Deprivation and time of year

Prevalence did not appear to vary with deprivation, month of the year or GP surgery.

NICE identified two studies which found that UTI was more common in the summer months.[1 181 182] I expected UTI prevalence to be greater in the summer months because I was measuring the proportion of children with acute illness who had UTI and in the winter months I would expect there to be greater numbers of children presenting with URTI and other viral illness which would therefore result in proportionately less UTI. The swine flu epidemic may have been partially responsible for my lack of seasonal variation. The epidemic started earlier in the year than the usual winter flu peak, the advice throughout the epidemic period was to stay at home and not to present to the surgery (where possible) and surgeries were very busy with the epidemic and contingency plans and study recruitment in general was lower than expected.

Laboratory variation

There was a suggestion of some differences in prevalence according to laboratory, however numbers were too small to determine whether this was significant.

The UTI prevalence varied between the four laboratories but these were associated with wide confidence intervals apart from laboratory 1 which received most (84%) of the urine samples. Laboratory 2 had the lowest prevalence (0; 95% CI: 0-17.6%) and this was the laboratory with a SOP of not culturing microscopy negative urine samples. Laboratories 3 and 4 had higher 95% confidence intervals for prevalence than the other laboratories. There were no obvious reasons in their SOPs to explain this. It may be due to chance with low numbers of urine samples analysed by these laboratories. When the three other laboratories were considered as one group and compared to laboratory 1 the prevalence was higher (10.4%) as a group, but the confidence intervals overlapped with laboratory 1 (5.8-18.1% compared to 3.4-7.3% for laboratory 1).

Urine sampling method

431 (72%) indicated which method of urine sampling was used. Nappy pads were used in the majority of children less than three years old (100% aged <3 months; 74% aged ≥ 3 months to <3 years). Clean catch collection was used in all children ≥ 3 years old. There was no statistically significant difference in the prevalence of UTI between nappy pad and clean catch samples (p=0.19) There was no statistically significant difference in the prevalence between nappy pad and clean catch samples for children under 3 years old (p=0.76).

I was surprised that there was no difference in the prevalence of UTI according to sampling method. I expected the prevalence in nappy pad samples to be higher due to the higher probability of contamination, and possible false positive results (thus 'misallocation bias'), and also because the children using nappy pads were younger. When children under three years old (those in whom both nappy pads and clean catch methods were used) were considered separately, there was still no statistical difference in the prevalence of UTI, although the trend was towards fewer UTIs in those using nappy pads than those using the clean catch method. This may indicate that nappy pads, with the higher levels of contamination, may have higher levels of false negative results.

UTI threshold and borderline results

The definition of UTI was a pure or predominant growth of bacteria of >10^5 cfu/ml on culture of urine. In addition to the 5.9% which fitted this criterion, a further 1.8% had a pure or predominant growth of bacteria of between 10^4 and 10^5 cfu/ml and 1.0% had predominant growths of >10^5 cfu/ml of two bacteria.

I discussed the results with microbiologists (Dr Robin Howe and Dr Mandy Wootton) at Cardiff and Vale LHB and they felt that the pure or predominant growth of between 10^4 and 10^5 cfu/ml of a single bacterial species and predominant growths of >10^5 cfu/ml of two bacteria, although negative by current definitions of UTI may be interpreted as possible UTI depending on clinical findings.

The National Laboratory Standards document for 2012 states, "[children] colony counts of $\geq$ 10^3 cfu/ml of a single species may be diagnostic of UTI in voided urine.[89] Generally a pure growth of between 10^4-10^5 cfu/ml is indicative of UTI in a carefully taken specimen." This document would also classify the growth of 2 bacteria each with a growth of >10^5 cfu/ml or one with a growth of >10^5 cfu/ml and one with a growth of 10^4-10^5 cfu/ml as positive if there were WBCs on microscopy or if the child were symptomatic.[89]

Some authors have suggested a lower threshold for the diagnosis of UTI.[16 88 109] Kanellopoulos et al (2005) found that UTI could be present despite low bacterial counts and that these were more common in young children, often caused by non-*E.coli* bacteria but associated with the same risk of scarring as in higher count infections.[16] Others have argued that the presence of more than one organism should not necessarily rule out UTI and that mixed infections may occur.[90 107] If the 'borderline' urine results from my study were considered UTIs, the prevalence of UTI would be 8.7%.

There are not sufficient data from my study to suggest whether the threshold should be changed. Further studies investigating the development of renal scarring at different diagnostic thresholds, and ideally long term follow-up are needed. The clinical outcomes of children with borderline or lower threshold results may inform the discussion. If the outcomes for these children were more similar to the outcomes of children with UTI than those without, it may suggest the need for a change in the diagnostic threshold. I found no significant differences in the outcomes of children with UTI, with borderline results or with

negative results with respect to the number of re-consultations, acute admissions, out of hours or A+E contacts or hospital referrals in the six months following the index consultations, but numbers were small.

Children who had a UTI at the index consultation were more likely to have two or more courses of antibiotics in the subsequent six months of follow up than those who did not have a UTI (p=0.02), but this was not the case for those with borderline results. Children with borderline results did receive investigations of the renal tract more often than those with negative results.

Further studies are needed to determine the nature of the clinical illness with both short-term and long-term outcomes for children with these 'borderline' results.

Mixed growths and contamination

Mixed growths were reported in 48.4% samples. A heavy mixed growth of >10^5cfu/ml was reported in 34.8%. Some laboratories commented on reports that mixed growth was likely to represent contamination. Heavy mixed growths were more common in nappy pad samples (61.7%) compared with clean catch samples (13.2%; p>0.01).

There was no statistically significant difference in the prevalence of UTI between nappy pad and clean catch samples both for all children (p=0.19), and for children under 3 years old (p=0.76).

Giddens (1998) found a contamination rate of 66% in children under 2 years which is similar to my finding of heavy mixed growths among nappy pad samples of 61.7%.[86]
That there was no difference in UTI prevalence between nappy pad and clean catch samples is interesting as it is widely believed that the increased contamination of nappy pad samples will result in more false positive results. All the nappy pad samples were from children less than 3 years old. I found that there was a higher proportion of heavy mixed growth in nappy pad samples as I had expected, but the prevalence of UTI was 5.5% in nappy pad samples and 6.6% in clean catch samples in the children less than 3 years old, with no statistical difference in the prevalence. This is surprising if the hypothesis that nappy pad samples result in more false positive results is true. It seems more likely from my data that nappy pad samples, growing more mixed cultures, result in a higher chance of false negatives with true

positives hidden by contaminating bacteria. Interestingly, there were also higher levels of leukocytes and nitrites in the urine samples collected with nappy pads ($p=0.05$ and $p<0.01$ respectively) but no corresponding higher rates of UTI by culture ($p=0.19$). Lau 2007 comments that contamination may cause false negative results in infants.[90]

No culture for microscopy negative samples

Urine samples were not cultured in 40 (6.7%) cases.

Some of these were due to laboratory 2 (12) whose SOP clearly stated that it did not culture urine with negative microscopy. Those not cultured constituted 66.7% of samples received by this laboratory. Laboratory 1 did not culture 26 (5.2% of all samples received by this laboratory) and laboratory 3 did not culture 2 (3%). This seemed to be a variation from the normal SOP in these laboratories where urine was cultured in children irrespective of microscopy results. However, laboratory 1 began to use an automated microscopy machine (flow cytometer) part of the way through the study and if no bacteria were detected by flow cytometry, the urine was not necessarily cultured in children. According to the laboratory SOP and the National Laboratory Standards for analysis of urine (2012), children should have continued to have urine cultured irrespective of microscopy results.[89] The National Laboratory Standards document states that, "urine analysers may be used to screen for 'negatives' to allow earlier reporting. Regardless of screening result, culture is still recommended for all specimens from children".[89]

There is evidence that microscopic detection of *white blood cells* (pyuria) is not reliable in the detection of UTI in children.[112] On the one hand, UTI can occur without significant pyuria[112] and on the other hand, white blood cells can be detected in the urine of children with fever from other illnesses.[183] Microscopy to detect *bacteriuria* is a better predictor of UTI than microscopy to detect pyuria but still has low sensitivities.[1 112]

NICE conducted a review of other diagnostic tests including flow cytometry (automated microscopy) and concluded that there was insufficient evidence to determine the accuracy of this.[1] I found several reports comparing automated microscopy with culture. Sensitivities ranged from 64% - 98% and specificity 55% - 92%[184] All of these were conducted on adult populations. I found one paper which considered the accuracy of automated microscopy in urines from children.[185] They included 168 urine samples and reported a sensitivity of 89%

and specificity of 85% overall, and a sensitivity of 100% and specificity of 83% in children under the age of three years old. But only 14 children were under the age of three years old, two of whom had positive culture and they also found that urinary dipsticks had 100% sensitivity for this group which has been shown by larger studies not to be an accurate method.[112] Interestingly in this paper, these authors from a UK lab, report that their standard practice for paediatric samples is to not culture dipstick negative urine despite pointing out in their introduction that "the NICE guideline recommended manual microscopy in those under 3 years of age and urine dipstick in those over 3 years of age".[185] The NICE guidelines recommend microscopy in those under 3 years of age *in addition* to culture in all children irrespective of microscopy results.[1]

Laboratory procedures

The variation in laboratory procedures and adoption of new techniques which may not be validated for all populations is quite striking to me. Out of the four laboratories involved in my study, one had a SOP of not culturing microscopy negative urine which seems to be at odds with current guidelines; and one laboratory began using a method which does not appear to be adequately assessed or validated in children. There is a clear need for standardisation of laboratory procedures for the diagnosis of UTI in children and a robust process for assessing accuracy and validity of new methods and equipment before they are adopted by laboratories.

Causative organisms

I found that the most common bacteria cultured were E.coli. These were responsible for 54.2% of UTIs. An additional 22.9% were reported as Coliform. More than half of the E.coli (57.9%) and 37.5% of the Coliform were resistant to 1 or more antibiotic.

Most studies report that most UTIs are caused by *E.coli*, both in adult and paediatric populations.[91] However, only 54.2% of UTIs in my study were *E.coli* which is a lower proportion than most other studies in the literature, with most studies finding that more than 70-80% of UTIs in children are due to *E.coli*.[93-95] Escherichia is a type of coliform (along with Klebsiella, Enterobacter, Citrobacter and others) and although it is usually identified by laboratories, it is likely that some of the *E.coli* UTIs were identified as 'coliform' but no further, reflecting further variation in laboratory analysing and reporting procedures.

Most published studies did not involve systematic sampling of urine and included much older children (up to 16 years old). My study includes children who would not have been identified in previous studies without systematic sampling. One study with systematically sampled urines from very young infants found that the most common bacteria causing UTI was coagulase negative staphylococcus.[96] Most of the non-*E.coli* UTIs in my study were in children less than three years old (79.2%). Other studies have found that the younger children are more likely to have non-*E.coli* UTI.[94 96 98]

Coagulase negative staphylococcus is often considered to represent contamination but is a recognised uropathogen in children, particularly in very young infants, often associated with instrumentation of the urinary tract.[89 96] The distinction between uropathogenic and non-uropathogenic bacteria is not always clear.[89] There is not a clear set of uropathogens versus non-uropathogens as bacteria which are commonly found as skin or gut commensals (and therefore possible contaminants) can sometimes be the cause of UTI. Finding a low growth of one of these organisms is likely to be as a result of contamination, but a high, pure growth may represent a UTI, particularly if the specimen is known to have a very low likelihood of contamination (e.g. from a suprapubic (SPA) specimen), if there is a high degree of suspicion of UTI (e.g. suggestive symptoms or high WBC count) or if the child is in a group known to have a higher risk of UTI from this sort of organism (e.g. has undergone instrumentation of the urinary tract or is a very young infant). Categorising bacteria as uropathogens or not *with certainty* is not possible using currently widely available methods.[89]

More than half the *E.coli* cultured in my study was resistant to at least one antibiotic. This was higher than I expected. The UTIs diagnosed in my study are from systematically sampled urines from ill children in primary care. These include children with UTI who may not have been identified had their urine not been systematically sampled. Therefore these UTIs would probably represent the less severe, perhaps self-limiting cases which would have been unrecognised, compared with the UTI usually diagnosed when a clinician suspects UTI or who are more severely ill or with recurrent UTI. For this reason, I suspect that the resistance rate of bacteria found in my study would be lower than normally found.

Empirical antibiotic prescription

Antibiotics were prescribed at the index consultation (prior to urine culture results) in 37.1% children subsequently found to have a UTI and in 27.8% of those who did not have UTI. Antibiotics were most frequently prescribed for presumed respiratory tract infections. Antibiotics were more likely to be prescribed if the GP suspected UTI (p<0.01).

Overall, 28% children were prescribed antibiotics at the index consultation, which is similar to other studies of acutely ill children presenting in primary care.[178 186]
Approximately half of those thought to have UTI by the GP were prescribed antibiotics at the index consultation (prior to the result being available). I was surprised that half of those who the GP thought may have UTI were not prescribed antibiotics at the index consultation. It may reflect an uncertainty with the diagnosis even when it is considered. Perhaps they have considered that it is enough of a possibility to request a urine sample but not sufficiently likely to justify antibiotics until the culture result becomes available. It may be that GPs were more likely to suspect UTI or indicate it as a working diagnosis because they were taking part in a research study concerning UTI rather than a reflection of normal practice.

Appropriate antibiotics (i.e. ones which would have treated the infection) were prescribed at the index consultations in 6/7 of those who had UTI and who were suspected of having UTI by the GP. In the 28 with UTI who were not suspected of UTI, only 1 had an appropriate antibiotic prescribed at the index consultation.

It is important to recognise that if GPs did not suspect UTI, only 7% received appropriate antibiotics at the index consultation compared with 85.7% if GPs suspected UTI.

Presumably those children with UTI who were not prescribed appropriate antibiotics at the time of the index consultation would have received them once the culture results were received by practices, but unfortunately I did not collect those data. If antibiotics are prescribed at the initial consultation (prior to urine culture results), unless UTI is suspected by the prescribing clinician, it is unlikely to be effective in treating a UTI.

An important issue is whether antibiotics started a few days after the index consultation (or onset of symptoms), as would have been the case for the majority of children with UTI in my study, prevent the development of renal scarring and long term complications. This is not

clear, although there is some evidence that a delay in treatment of an acute UTI is more likely to result in renal scarring.[24-28] One systematic review found that a delay of 4-7 days increased the risk of renal scarring.[23] Culture results generally take 2-3 days to reach the GP so if the urine is sampled promptly, the result communicated to GPs quickly and the antibiotic treatment is initiated immediately following the culture result, then perhaps this will be sufficient to reduce renal scarring.

More research is needed both in determining how quickly antibiotics need to be administered following onset of symptoms to prevent renal scarring and in reducing the delay in diagnosis of UTI. The development of fast, accurate diagnostic testing could improve the situation dramatically. In the meantime, working within the current situation, it may be that awareness of the need for prompt urine sampling and antibiotic therapy needs to be enhanced among clinicians and parents. There is likely to be variation in symptom duration prior to consulting and GPs generally encourage parents not to consult with their child for common self limiting illnesses. The question is, should we encourage parents to consult earlier so that urine can be sampled earlier? Raising awareness of the need for prompt urine sampling and high suspicion of UTI (and therefore consulting) may result in large increases in early presentations of children.

Symptoms and signs

A multivariable logistic regression model identified age range, pain or crying on passing urine and increased urinary frequency (or frequency of wet nappies) as being associated with UTI. A history of fever or absence of an alternative site of infection was not significantly associated with UTI.

Urinary symptoms

I was quite surprised that the predictive symptoms and signs which came out of the multivariable logistic regression model were urinary symptoms. Published studies and guidelines highlight that symptoms tend to be non-specific in children.[1 48 58 72] In fact, the most common presenting symptoms in children with UTI in my study were also non-specific. The three most common presenting symptoms were being irritable or grouchy, being clingy, and poor feeding. However, they were also extremely common in children without UTI. Only 11% of those with UTI had increased urinary frequency and only 14% had pain or crying on passing urine.

It is likely that these urinary symptoms were difficult to establish in the youngest children and the model may be less useful in these children. It is also likely that any clinical decision rule which includes urinary symptoms will therefore be difficult for clinicians to use as these symptoms will be harder for parents to determine in the younger age groups. It is also important to note that my sample probably under-represented the younger children.

As described earlier, the multivariable model was overall a poor fit for my data with much variability not explained by the model. Further, much larger studies are needed to determine whether any symptoms or signs can be used to predict or rule out UTI in children with any accuracy. My results suggest that in order to detect UTI, urine would need to be sampled from the majority of children irrespective of their presenting symptoms or examination findings. I have proposed a urine sampling strategy in which urine samples are omitted in older children without urinary symptoms but this would need to be externally validated in another study.

Fever

The study was not powered to detect the predictive value of symptoms and signs accurately. The univariable analyses need to be interpreted with caution due to the large number of tests. However, it is striking that a history of fever was not associated with UTI. Temperature measured in surgery as a continuous variable was also not associated with UTI. When fever measured in surgery was dichotomised to $\geq 38^{o}C$ and $<38^{o}C$, there was possibly an association with UTI (p=0.08) but less than half of the children with UTIs had a temperature of $38^{o}C$ or above. This is important because the majority of published studies include only children with fever and current guidelines highlight the importance of urine sampling in children with fever.[1 48 60 63 65-68 70 71 73 83 100-103 151 152 154] Other studies have also found that fever is not necessarily present with UTI and importantly that fever cannot be used to predict renal scarring.[81]

Alternative source of infection

Current guidelines state that urine sampling is not required if there is evidence of a potential alternative source of infection (initially).[1] An 'alternative source of infection' has been defined differently in studies and sometimes not defined at all.[48 60 68 71 103 154]

I found that there was no difference in prevalence of UTI between children with and without an alternative site of infection (p=0.64).

Looking only at abnormal examination findings rather than clinician working diagnosis, I found that children with UTI were just as likely as those without to have an abnormal chest, throat, or abdominal examination (p=1.00; p=0.97;p=0.39 respectively). Statistically, there was also no difference between UTI and non-UTI groups for abnormal ear examination (p=0.16). However looking at the crude numbers (2.9% in UTI group vs. 10.9% in non-UTI group), this may be a type 2 error with the small numbers hiding a true association. A larger study is needed to look more closely at this.

The finding that UTI cannot be ruled out on the basis of the presence of an alternative site of infection is important. UTI will be missed if urine is not sampled from these children. Other studies have also found that the presence of an alternative source of infection cannot reliably rule out UTI.[48 68]

Proposed urine sampling strategy

Using the multivariable model, the probability of UTI in children less than three years old, irrespective of presenting symptoms and signs, was >5%. In children aged three-to-five years, with neither pain on passing urine nor increased urinary frequency, the probability of UTI was 2%.

It is not clear what level of prevalence of UTI should warrant universal urine sampling from ill children. The balance of costs and benefits is complex.

A survey of paediatricians found that most considered a prevalence of more than 3% in a population of children to be sufficient to justify universal urine sampling in that population.[40] However, this study was conducted in 1983 and opinions about UTI in children may have changed. In addition, the concerns of paediatricians, and the feasibility of universal urine sampling in their setting, may be different to those of GPs, microbiologists, health economists or policy makers. However, it is a useful benchmark to consider.

A possible strategy of sampling urine in all children under the age of five years old except those three years or older without urinary symptoms was considered. This proposed

strategy was compared with the urine sampling strategy in the NICE guidelines and with urine sampling according to GP suspicion of UTI. I found that the proposed strategy would identify 97% of UTIs and would only miss 3% of UTIs, compared with 51% which would be missed if NICE guidelines were followed and 80% if sampling were based on GP suspicion alone.

This gives a sensitivity of 20.0% and specificity of 94.0% for UTI with sampling based on GP suspicion; a sensitivity of 48.6% and specificity of 61.0% with sampling based on NICE guidelines; and a sensitivity of 97.1% and specificity of 32.4% following my proposed sampling strategy. The decision (decision rule) on whether to obtain a urine sample from an ill child needs to have a high sensitivity, even at the expense of specificity.[177] At this stage we only want to omit a urine sample in children whom we can be reasonably sure do not have a UTI. Subsequent testing, perhaps with urinary dipsticks or microscopy or laboratory culture, will need a high specificity as well as high sensitivity.

My proposed sampling strategy would involve sampling urine from twice as many children than is currently recommended by NICE guidelines and ten times more than would be if sampling were based on GP suspicion alone. This clearly has huge implications in terms of equipment, processing costs and time costs. These costs occur at two main points, firstly at the time of consultation in the GP surgery, and secondly when the urine sample is sent and processed by the laboratory.

Given that urinary dipsticks, as the only commonly used near patient test, have questionable accuracy in children, currently all urine samples should be sent for laboratory microscopy and culture for the diagnosis of UTI in children.[1] With the development of more accurate near patient testing this may not be necessary in the future, and the cost and time associated with laboratory culture techniques may be reduced. However, without the initial collection of a urine sample, whatever new diagnostic tests there are, UTI will not be diagnosed in most children because the presenting symptoms and signs cannot be reliably used to rule out UTI. It seems likely that the time and cost associated with obtaining a urine sample in primary care is necessary now and in the future *if* we want to improve the diagnosis of UTI.

Feasibility of obtaining urine samples

In addition to the cost, there is the issue of whether it is actually possible. My proposed sampling strategy would require urine samples at initial presentation from 69% of acutely ill children under five years old. I only obtained a 70% urine retrieval rate, even when practices were being reimbursed for their time and incentivised to obtain the urine sample. It was much more difficult to obtain urine samples in the younger children, all of whom would require a sample if this sampling strategy was followed. I also found that it was much less likely that a urine sample was received within 2 days if it was not obtained at the surgery ($p<0.01$) and this has implications for GPs in terms of space and access to nurses.

GPs and parents would need to be informed and convinced of the need; appropriate sampling equipment would need to be more readily available; time and room at the surgery to obtain the sample, and nursing staff availability may also be necessary. Some financial support may need to be considered in order to change GP sampling behaviour (investment in training and education). A UK survey of GPs found that practical difficulties of urine collection and concerns about the costs of investigations were important barriers to detecting UTI.[41] In addition, advising parents to bring their child to the surgery promptly for non-specific symptoms in order to obtain urine samples contradicts current advice for common, self-limiting illnesses and would need to be carefully considered.

Cost to the NHS

The costs and implications of increased urine sampling and processing of samples needs to be considered. There are the costs of the equipment to obtain urine samples, the costs of GP or nurse time to support obtaining the sample, the laboratory costs of processing and reporting the sample; the costs of further patient contact to discuss results and advise on management; the costs of increased antibiotic use (including side effects and contribution to antibiotic resistance), and the costs of further investigations. The costs need to be weighed up against the potential benefits of diagnosing more UTIs, and providing prompt antibiotic treatment, with the possible benefits of reducing long-term complications associated with significant morbidity and NHS costs.

Whether it is worth the additional costs to the NHS, given that the association with long-term complications is far from clear and that UTI is often a mild and possibly self-limiting acute illness, is a matter for debate. Clearly, the authors of the NICE guideline in 2007 felt that it

was sufficiently important to recommend increased urine sampling and prompt diagnosis and treatment; and significant cost savings may be made if expensive investigations and long-term complications can be avoided.

Further evaluation of my proposed sampling strategy is needed in another data set for external validation and modelling of economic implications. This may be possible with another study which I am involved in (the 'DUTY' study) which is a large dataset of acutely ill children under five years old also with systematically sampled urine.

The views of GPs and parents should also be sought.

Illness duration

Of the children diagnosed with UTI and with 2 week follow-up data (n=18), 9 (50%) had an illness which lasted more than 2 weeks after the index consultation. None had been admitted to hospital.

I was surprised that there were so many with an illness lasting beyond two weeks. This was reported by parents and their definition of illness will vary. The question I asked was whether their child had completely recovered from their illness and if so for how many days had it lasted. The numbers are small and I have not got information on those who did not have UTI for comparison. It may be that the delay in waiting for the urine sample result and subsequent delay in antibiotic prescription contributed to the length of illness. It would have been useful to have further data on which symptoms were ongoing, when antibiotics were started, repeat culture results to see when resolution of bacteriuria occurred and how this corresponded to symptoms. Further research studies are needed to explore this further.

Outcomes

Among the children with 6 month follow up data (n=28 with UTI; n=487 without UTI), there was no difference in the number of re-consultations with GPs, number of acute admissions, number of out of hours or A+E contacts or number of hospital referrals between those with and those without UTI in the 6 months following the index consultation. Children with UTI were treated with more courses of antibiotics than those without, with children who had a UTI nearly twice as likely than those without to have received two or more courses of antibiotics in the subsequent 6 months (p=0.02).

These findings suggest that increasing the detection of UTIs will not necessarily increase the use of NHS services (apart from the antibiotic prescriptions). I had expected that there would be a higher consultation rate among children who had been diagnosed with UTI as I thought that parents would be more likely to bring their child with any further illness in case it was another UTI. I also found it surprising that the number of hospital referrals was not greater in the UTI group as the guidelines recommend specialist imaging in some of those children. It may be that the referral rate will increase as awareness of the guidelines increases. The numbers of children with UTI followed up is fairly small. Larger studies may detect differences in consulting behaviour in children who have had UTI compared with those who have not.

Imaging and NICE guidelines

Of the children diagnosed with UTI with 6 month follow-up data (n=28), 3 children had been referred for or had an USS and 1 child had received a DMSA scan. No children had been referred for or received an MCUG. Comparing the investigations which children received with those advised by the current NICE guidelines, showed that only 1/16 recommended children received an USS and none of the 13 recommended received a DMSA scan. The one child in whom an MCUG was indicated did not receive one.

Only one child (the one who had an USS) was referred to the hospital during the six month follow up period.

I was surprised at the lack of adherence to guidelines for follow-up. Perhaps clinicians did not believe that the UTI diagnosed in this study represented true UTI. They may have felt that as they would not have normally sent a urine sample, for many of the children, and did not clinically suspect UTI, that it was unlikely to be a UTI even if the result was positive. They may have felt that it was more likely to be a false positive caused by contamination.

It may be that clinicians were unaware of the NICE guidelines. I did provide a summary of NICE guidelines for all the practices involved in the study and highlighted these during the training of practices, however the guideline is long and quite complicated. I was surprised that children were not referred to paediatricians for follow-up investigations even if these were not arranged by the GPs.

I think part of the problem may be that the guidelines are confusing. In the summary section for imaging strategies (p11), it states, "children with cystitis/lower urinary tract infection should undergo ultrasound (within six weeks) only if they are younger than 6 months or have recurrent infection."[1]

However, when looking at box 6.14 (p12): *Recommended imaging schedule for infants and children 6 months or older but younger than 3 years* in the NICE guideline, ultrasound during the acute infection is recommended for atypical UTI.[1] Atypical UTI includes children who have infection with non-*E.coli* organisms as well as more serious illness. This probably needs to be emphasised to GPs and also laboratories need to report the type of organism more accurately than simply 'coliform'.

Two children received an USS and one child a DMSA scan when this did not seem to be indicated by NICE guidelines. It may be that these tests were indicated in these children but that I was unable to identify these criteria. Perhaps they had other features which defined them as 'atypical' UTI (for example septicaemia or failure to respond to treatment with suitable antibiotics within 48 hours).

Summary of specific points relating to current guidelines

1. The most common presenting symptoms and signs of UTI in children in primary care are non-specific.
2. Urinary symptoms may be helpful in determining which children should have their urine sampled in those over the age of three years but not in younger children.
3. UTI is not more frequent in those without an obvious source of fever.
4. UTI is not more frequent in those with a fever than those without among acutely ill consulting children.
5. Current guidelines appear to be poorly adhered to in terms of urinary sampling in primary care and imaging of children diagnosed with UTI. This may be partly due to the complex nature of these aspects of the guideline.
6. There is a need for standardisation of laboratory storage, analysis and reporting procedures.

These points should inform the next revision of the NICE guideline for urinary tract infection in children due in August 2013.

Dissemination of research

I have published the main findings of my research in the British Journal of General Practice (see Appendix A2).[150] I have discussed my findings with other General Practitioner colleagues and presented the findings to the DUTY study management group. I have also presented my research at the conferences of the Society of Academic Primary Care (SAPC) and the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA).

Summary of further research needed

Throughout the discussion I have mentioned areas where further research is needed. In this section, I have brought these points together as a summary of future research priorities in this field.

- External validation of the model and proposed sampling strategy (possibly using the 'DUTY' dataset).[176]
- Economic modelling of the sampling strategy.
- Exploration of the views of parents, GPs, microbiologists and paediatric nephrologists about widespread urine sampling in children and prevalence thresholds which warrant this; feasibility and barriers to such a strategy; and needs for training and equipment provision.
- Evaluation of adherence to and effectiveness of current (NICE) guidelines, particularly with regards to urine sampling in primary care and imaging following confirmed UTI. Exploration of the views of clinicians on the guidelines and barriers to implementation.
- Further prospective studies with systematic urine sampling in ill children from A+E and OOH departments, including those with an alternative site of infection and a temperature of $<38^{o}$C.
- Larger studies to further explore whether specific symptoms, signs, or risk factors may be used in combination to determine the probability of UTI with sufficient accuracy to enable more targeted urine sampling.

- Larger prospective studies with clinical outcomes to determine the optimal diagnostic threshold for UTI in children using current standard culture methods.
- Further investigation of low growth, mixed growth and 'contaminated' samples with assessment of immune function and identification of bacterial species and clinical outcomes to determine whether these are 'hiding' true UTI.
- Further clarification of the definition of terms such as 'predominant growth', 'uropathogen' and 'contamination' by laboratories.
- Investigation of laboratory variation in the process and reporting of urinary specimens and agreement/adherence with national standards.
- Long term follow up studies of children with UTI, including those previously unrecognised but now identified from systematic urine sampling, to determine the risk of complications such as adult or recurrent UTI, renal scarring, hypertension, pre-eclampsia and end-stage renal failure. Exploration of the optimal diagnostic threshold for culture for detecting children at risk.
- Effectiveness of antibiotics at preventing progression to long term complications and determination of how soon after onset of symptoms and presentation to the GP these need to be taken to be effective. Initial studies could use renal scarring in the short term as a marker for long term complications.
- Further exploration of bacterial species grown on culture using DNA techniques (PCR pyrosequencing) and comparison between healthy children, those known to have UTIs and those with mixed growth or negative culture results to determine whether bacterial species which grow less well with standard culture methods may be uropathogenic in children.
- Investigation of potential urinary biomarkers for UTI (e.g. immune system mediated chemicals (cytokines)). There is a need for a quicker and more accurate diagnostic test for UTI.

My priorities for future research would be:

1. External validation of my proposed sampling strategy
2. A cluster randomised trial with an educational intervention (for GPs, nurses and parents) aimed at increasing urine sampling and diagnosis of UTI in primary care
3. A long-term follow-up study of children with UTI identified through systematic sampling to determine which children develop long-term complications.

Conclusions

I have achieved the main aim of my research which was to determine the prevalence of UTI in acutely ill presenting children in general practice. I have also increased the understanding of UTI in terms of the presenting symptoms and signs, management by GPs and clinical outcomes (up to six months) and addressed all of my research objectives (Table 6.2)

Table 6.2: Research objectives

Research objective	
1	Conduct a systematic review of the literature concerning the prevalence of UTI in children in primary care.
2	Conduct a pilot study to determine the feasibility of recruiting, and obtaining samples from, ill children in primary care.
3	Conduct a study to determine the prevalence of UTI (defined as $>10^5$ organisms/ml of urine) in children aged before their fifth birthday presenting to primary care with an acute illness of less than or equal to 28 days duration.
4	Determine the predictive value of symptoms, signs, risk factors and point of care dipstick tests in predicting positive urine culture (UTI) in urine samples systematically obtained from acutely ill children in primary care.
5	Develop a decision support system and sampling strategy for use in primary care for the diagnosis of UTI in children.
6	Describe hospital referral, hospital investigation, re-consultation in primary care and UTI rates at 6 months for children found to have a UTI at initial consultation compared with those without UTI.

I have identified some of the problems with current practice and shown that urine sampling based on GP suspicion or according to current NICE guidelines is likely to miss the majority of UTIs.

I have proposed a urine sampling strategy which would increase the identification of UTIs but this would result in large increases in urine sampling and needs external validation and economic evaluation.

I have found that the NICE guidelines are not followed in terms of follow up for children with UTI. More research is needed to understand the reasons for this.

I have shown that there is variation in laboratory methods and a need for standardising methods and reporting.

I have explored some of the controversial issues and highlighted the need for further research. In particular, how important is it to correctly diagnose UTI; does it really lead to long-term complications and in which groups of children; how promptly does it need to be treated to prevent renal damage; will increasing urine sampling reduce the long-term complications; will this be a cost-effective strategy in the long term; and are current methods correctly identifying true UTI?

It is of great importance to understand the association between UTI in childhood and long term complications and the ability of treatment to prevent these. The decision to advocate widespread urine sampling in children hinges on this. If it were not so important to diagnose all the UTIs, perhaps if only those with severe or persistent acute illness were at risk of long term complications, then there may be less need to change current practice of clinician led urine sampling. Perhaps it would not matter if those with mild or self-limiting illness or in whom UTI was not suspected or recognised were not diagnosed. However, if there *are* long-term complications which can be prevented by prompt diagnosis and treatment of all (even mild or self-limiting) UTIs, then the levels of suspicion and urine sampling need to be raised significantly. Perhaps urine needs to be sampled routinely from all consulting ill children. Urine screening tests (e.g. dipsticks and automated microscopy) would need to have extremely high sensitivities for culture to be omitted and the diagnostic threshold on culture may need to be lowered if low-count bacteriuria were also found to be associated with long-term complications.

Long term follow up studies of children diagnosed with UTI, in primary care by systematic sampling, are needed. Further studies are needed to determine whether combinations of symptoms and signs can be used to predict which children have UTI or used to target urine sampling. In the absence of these studies, based on the available evidence, GPs should increase urine sampling in acutely ill children and ensure prompt antibiotic treatment and appropriate follow up for any children found to have UTI.

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Chapter 8: Appendices

Section A: Published papers

Section B: Appendices relating to the thesis

Section A: Published papers

A1: O'Brien K, Stanton N, Edwards A, Hood K, Butler CC. Prevalence of urinary tract infection (UTI) in sequential acutely unwell children presenting in primary care: Exploratory study. *Scandinavian Journal of Primary Health Care* 2011;29:19-22

A2: O'Brien K, Edwards A, Hood K, Butler CC. Prevalence of urinary tract infection in acutely unwell children in general practice: a prospective study with systematic urine sampling. *British Journal of General Practice* 2013; 63: 91-92

These papers are not included in the electronic version of the thesis due to the copyright of the journals.

Section B: Appendices relating to the thesis

Appendix 1: Appendices relating to Chapter 1: Background

Appendix 1.1: Cardiff and Vale Standard Operating Procedures for the Investigation of Urine

This is not included in the electronic version of the thesis due to copyright. It is available online:

HPA. UK Standards for Microbiology Investigations: Investigation of Urine. London: Health Protection Agency, 2012. [cited 2012]; Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317132858791.

Appendix 2: Appendices relating to Chapter 2: Systematic Review

Appendix 2.1: Tables 1-5 Comparison of studies to check for overlapping datasets and whether urine sampling was systematic

Appendix 2.1

Table 1: Comparison of Bonadio papers to check datasets were not overlapping

Paper	Date of publication	Dates of data collection	Study design	Age of included children	Exclusions and evaluation of systematic urine sampling	Sample size	Urine samples	Include ?
Bonadio[151] 'Relationship …'	1991	Jan – Nov 1990	Prospective	30-60 days (4-8 weeks)	"all received evaluation for sepsis [including urine]" Excluded children who had received antibiotic therapy within 72 hrs or antipyretic medication within 4 hours of presentation.	161	161 (100%)	✓
Bonadio(i) [64] 'Reliability… '	1993	Jan 1991 – Jan 1992	Prospective	0-8 weeks	Excluded children who were culture negative for bacterial pathogens & had received antibiotic therapy within 72 hours	233	233 (100%)	✓
Bonadio(ii)[65] 'correlating …'	1993	1983-1990	Retrospective review	0-8 weeks	Included infants "who received performance of a sepsis evaluation in the ED." However, "there were no instances in which a febrile infant younger than eight weeks did not received a sepsis evaluation during the study period"	1130	1130 (100%)	✓
Bonadio[66] 'The Clinical…'	1994	Jan 1989 – Jan 1993	Retrospective not clear which had culture/just dip	8-12 weeks	Excluded 1) infants who were culture negative for bacterial pathogens & received antibiotics within 72 hrs presentation 2) infants who had received antipyretic meds within 4 hrs presentation	367	321 (90%)	✓

Table 2: Gorelick and Shaw papers to check for overlapping datasets and sampling

Paper	Date of publication	Dates of data collection	Study design	Age	Temp	Exclusions and evaluation of systematic urine sampling	Sample size	Urine samples	Include
Gorelick	2000	Same data set as Shaw prevalence	Prospective	girls <2 years	≥38.3°C	Children with definite source of fever excluded but did include possible but not definitive sources (e.g. URTI, otitis, gastroenteritis) "the clinical policy in the ED was to obtain a catheter urine specimen for all boys<1 and girls <2 without a definitive or unequivocal focus of infection."	1469 girls (63 positive)	83% obtained. Clinical policy to obtain urines but not required for the study	X subset of Shaw
Shaw(i) prevalence of…	1998	Feb 1995-Feb 1996	Cross sectional. Urine cultures not prospectively requested. Clinical policy to obtain urines in the ED.	Boys <1 yr and girls <2 yrs	≥38.5°C	Excluded if taking antibiotics, immunosuppressed or had a definite source of fever on examination (meningitis, pneumonia, septic arthritis, cellulitis, adenitis, osteomyelitis, perf otitis media with exudate, scarlet fever, varicella, coxsackie diseae, measles, herpetic stomatitis, bronchiolitis, Kawasaki disease, HSP but included minor source (URTI, gasroenteritis, viral exanthema, otitis media) NB 1544 excluded from study. 26% due to antibiotics; 29% due to bronchiolitis	2908; 2411 with urine samples (80 positive results; 63 in girls)	2411 (83%) Those who had cultures were slightly younger & more likely to be described as 'ill appearing or toxic' with slightly higher temperatures. No difference in terms of sex, race, or presence of another source of infection	✓ Policy to obtain on all children and >80% children sampled
Shaw(ii) Screening	1998	Dec 1994 – Feb 1996	Cross sectional	Boys <1 yr Girls <2 yrs	Fever ≥38.3°C without source or suspected UTI	"clinical practice in the ED is not obtain urine cultures on boys<1 yr and girls<2 yrs if they do not have a definite source for their fever or do have UTI symptoms	(105 positive)	3873 cultures sent but don't know how many were requested. Denominator not given.	X denomin-ator not known

Table 3: Zorc and Levine to check for overlapping datasets

Paper	Date of publication	Dates of data collection	Study design	Age of included children	Temp	Exclusions and evaluation of systematic urine sampling	Sample size	Urine samples	Include
Zorc	2005	Oct – March 1999-2001 "detailed methods have been published previously (i.e. Shaw)"	prospective	≤60 days	Rectal temp ≥38°C	Excluded if received antibiotics within 48 hours of presentation. Standardized lab evaluation on all enrolled infants (including urine sample)	1025	1005 (98%)	X – subset of Levine
Levine	2004	Oct – March 1998-2001	prospective	≤60 days	Rectal temp ≥38°C	Excluded if received antibiotics within 48 hours of presentation. Standardized lab evaluation on all enrolled infants (including urine sample)	1248	1227 (98%)	✓

Table 4: Hoberman – more detail to assess sampling

Lead author	Design	Age	Other inclusion criteria	Sample size	Number urines samples (%)	Prevalence	Include?
Hoberman	Prospective. Urine in all infants ≤ 2months. For older children the urine was obtained according to the discretion of the clinician but was obtained in addition if an investigator was available (not at night or weekends)	≤ 1 year	Excluded children who had received antibiotics or had catheterisation in the previous 48hrs	2168 eligible.	945 (43.6%). NB this was 100% for 306 ≤2 mth olds – So 306/306 for <2 mth olds and (945-306)/(2168-306) = 34% for >2 month olds.	14/306 (4.6%) in <2 mths; 26/443 (5.9%) >2 mths in whom UTI suspected and 10/196 (5.1%) in whom not suspected. In white infants prev was 6.6%	Only include for <2 month olds as this systematic. For older children, not systematic (and only 34% sampled)

Table 5: Stanley more detail to assess sampling

Lead author	Setting	Design	Age	Temp	Sample size	Number urines samples (%)	Prevalence	Include?
Stanley	Paediatric ED. "Clinical guidelines recommend urine culture in ***most*** infants <3 months with fever"	Retrospective note review	<3 months	≥38.0°C but then looked at hyperpyrexic infants (≥40)	5273; 92 with temp ≥40°C included in study.	92/92 with fever >40 had urine cultures. Doesn't state what proportion of other included children had urine samples.	25/92 (27%) in hyperpyrexic infants. Overall 316/5273 (6.0%) but these may not have been systematically sampled	Only the 92 with fever ≥40°C. The rest not systematic sampling

Appendix 3: Appendices relating to Chapter 3: Pilot Study

Appendix 3.1: Consent form

Appendix 3.2: CRF

Appendix 3.3: Telephone follow-up questionnaire

Appendix 3.1: Consent form

Surgery code:
Patient Identification Number for this study:

CONSENT FORM

Title of Project:
EURICA: The Epidemiology of Urinary Tract Infection (UTI) in Children with Acute illness in Primary Care

Please initial box

1. I confirm that I have read and understand the information sheet dated December 2006 (Version 2) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my child's medical notes may be looked at by the research team from Cardiff University or from regulatory authorities where it is relevant to the research. This may include GP and GP out of hours notes, hospital and A&E notes. I give permission for these individuals to have access to my child's records. ☐

4. I agree for my child to take part in the above study. ☐

5. I agree to my GP being informed of the results of the urine tests and the participation of my child in the study. ☐

Name of Parent/Carer	Date	Signature

Name of Child

Name of Person taking consent	Date	Signature

1 for carer/parent; 1 for researcher; 1 to be kept with notes

December 2006
Version 2.

Appendix 3.2: CRF

EURICA: The Epidemiology of Urinary Tract Infection in Children with Acute Illness in Primary Care.

Please fax to Dr. Kathy O'Brien 029 2068 7219 when completed

Patient Registration Form:

Date of consultation:	

Patient identifiers and contact details:

Child's name	First:		Last:
Date of birth	Day:	Month:	Year:
Gender			
Parent/carer's name	First:		Last:
Relationship to child			
Address			
Telephone number			
Mobile number			

Patient eligibility (exclude if answer NO to any of the following):

Aged <5 years (before fifth birthday)?	Yes	No
Acute illness (≤28 days)?	Yes	No
First time in this study?	Yes	No
Written consent from carer to participate?	Yes	No

Exclusion criteria (exclude if answer YES to any of the following):

Radiological evidence of urinary tract abnormalities (X-Rays or scans including antenatal scans)	Yes	No
Taking regular, long term antibiotics (for≥28 days)	Yes	No
On chemotherapy (for cancer)	Yes	No
Currently taking oral prednisolone≥ 10mg per day (or equivalent) for ≥2 weeks	Yes	No

Patient eligible for study?	**Yes**	**No**

Consent obtained?	**Yes**	**No/declined**

Patient's symptoms (Nurse/Health care assistant/GP (Practice to adapt) to ask Parent/Carer):

Date of onset of illness	Day:	Month:	Year:

Symptom	**Present?**		
Nasal congestion/runny nose	Yes	No	
Cough	Yes	No	
Difficulty breathing or grunting	Yes	No	
Runny or blocked nose	Yes	No	
Flushed or hot or feverish	Yes	No	
Rash	Yes	No	
Irritable/cranky/not settling	Yes	No	
Clinginess	Yes	No	
Needing extra care	Yes	No	
Crying more than usual	Yes	No	
Not playing well	Yes	No	
Low energy/tired	Yes	No	
Not sleeping well	Yes	No	
Poor feeding/poor appetite	Yes	No	
Feeling sick	Yes	No	N/A
Vomiting	Yes	No	
Diarrhoea	Yes	No	
Constipation	Yes	No	
Abdominal pain/ tummy ache	Yes	No	N/A
Colic/grimacing/pulling up legs	Yes	No	N/A
Muscle aches or pains	Yes	No	N/A
Increased urinary frequency or number of wet nappies	Yes	No	
Smelly urine	Yes	No	
Dark or cloudy urine	Yes	No	
Pain/crying on passing urine	Yes	No	
Day or bed wetting when previously dry	Yes	No	
Poor weight gain	Yes	No	

Please list any other symptoms:

_____

_____

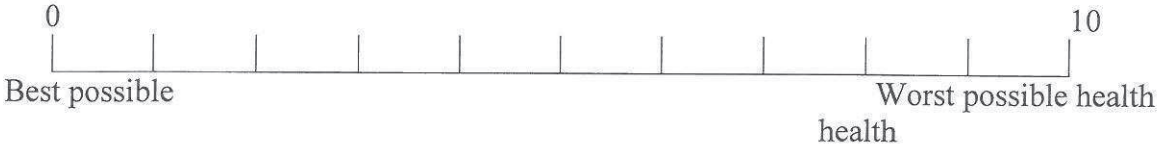
Was the temperature *measured* (by the parent/carer) at any time during this illness before coming to the doctor?

No	Yes

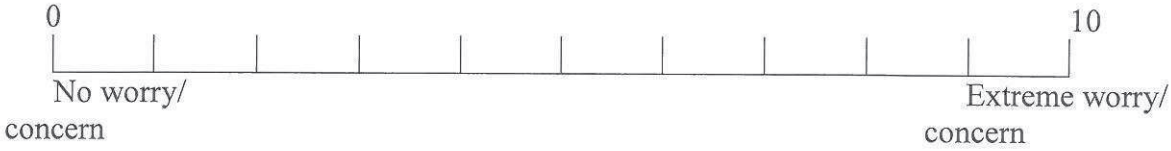
If YES, what was the highest temperature recorded by the carer/parent?

°C

Please ask the Parent/Carer to mark on this line, how *sick* they feel their child is today



Please ask the Parent/Carer to mark from 0-10 how *concerned* they are about their child's current illness



Examination (Nurse/Health care assistant/GP (Practice to adapt)):

Temperature (using infrared digital thermometer in ear)	°C
Pulse rate	/min
Respiratory rate	/min

Urine sample:

Date sample collected:	Day:	Month:	Year:
Time sample collected:			

Method of collection: please tick		
Not potty trained:	1st choice: Clean catch	2nd choice: Pad in nappy
Potty trained:	Clean catch	

Urine dipstick:					
Leukocytes:	Nitrites:	Blood:	Protein:	Glucose:	Ketones:

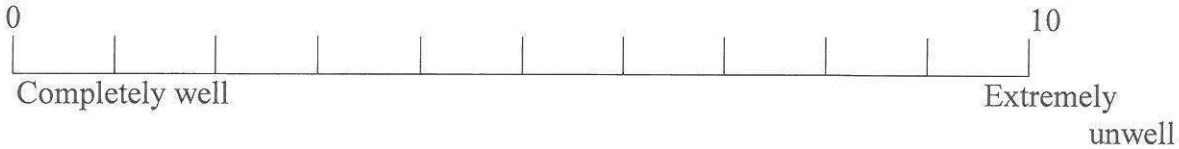
Please remember to send urine sample to laboratory: Please tick ☐

Examination (treating clinician: doctor/nurse practitioner):

Please circle:

Ears	Examined	Not examined						
			Right ear drum			Left ear drum		
	Normal		Yes	No	Not seen	Yes	No	Not seen
	Pink		Yes	No	Not seen	Yes	No	Not seen
	Obviously inflamed		Yes	No	Not seen	Yes	No	Not seen
	Discharge present in ear canal		Yes	No		Yes	No	
Throat	Examined	Not examined						
	Normal		Yes	No				
	Inflamed		Yes	No				
	Swollen/enlarged tonsils		Yes	No				
	Pus		Yes	No				
	Ulceration		Yes	No				
Chest	Examined	Not examined						
	Normal		Yes	No				
	Wheeze		Yes	No				
	Crackles		Yes	No				
	Using accessory muscles		Yes	No				
	Intercostal/subcostal recession		Yes	No				
Abdomen	Examined	Not examined						
	Normal		Yes	No				
	Tenderness		Yes	No				
	Other		Yes	No				
General	Normal		Yes	No				
	Rash		Yes	No				
	Meningism		Yes	No				

Please rate your overall impression of the child



What is your working diagnosis? _____

Management at this consultation (treating clinician: doctor/nurse practitioner)

Same day hospital referral?	No	Yes
Hospital referral but not same day	No	Yes

Did you prescribe any medication, including antibiotics?		Yes	No	
If yes, please state details				
Name:	Dose:	Times per day:	No. days:	
Name:	Dose:	Times per day:	No. days:	
Name:	Dose:	Times per day:	No. days:	

Would you have normally tested urine in this patient with a dipstick?	No	Yes

Would you have normally send urine for culture in this patient?	No	Yes

Information from Medical Records:

Has the patient ever been prescribed antibiotics before?	No	Yes

If yes, please give details:

Age of first ever course of antibiotics :	days	months	years
Total number of courses of antibiotics:			

Please list all antibiotics prescribed within the last year starting with the most recent:

Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:
Name:	Date:	Day:	Month:	Year:

Does the patient have a history of:

Urinary tract infection	No	Yes	Approximate date(s):
Kidney or bladder disease	No	Yes	Please specify:
Asthma	No	Yes	
Other lung disease	No	Yes	Please specify:
Diabetes	No	Yes	
Heart disease	No	Yes	Please specify:
Eczema	No	Yes	
Other (please specify)			

Please give details of any medication that this patient is currently taking and has been taking for ≥28 days

Name:	
Name:	
Name:	
Name:	
Name:	
Name:	

November 2006 Version 1

Appendix 3.3: Telephone follow-up questionnaire

EURICA: The Epidemiology of Urinary Tract Infection in Children with Acute Illness in Primary Care.

Telephone follow-up interview by researcher (at 21 days +/- 3 days after initial consultation)

Date of interview:	Day:	Month:	Year:

Patient identifiers and contact details

Child's study number		
Child's name	First:	Last:
Carer's name	First:	Last:
Relationship to child		
Telephone number		
Mobile number		

Just to remind you, the day your child saw the doctor was_____

Age of child _____

Symptoms

Would you consider that your child has completely recovered from this illness?	Yes	No

If Yes, how many days did the illness last – until complete recovery?

If No, please give details about continuing symptoms:
(interviewer will note those present, but not necessarily ask about each one)

Symptom	**Present?**		
Nasal congestion/runny nose	Yes	No	
Cough	Yes	No	
Difficulty breathing or grunting	Yes	No	
Runny or blocked nose	Yes	No	
Flushed or hot or feverish	Yes	No	
Rash	Yes	No	
Irritable/cranky/not settling	Yes	No	
Clinginess	Yes	No	
Needing extra care	Yes	No	
Crying more than usual	Yes	No	
Not playing well	Yes	No	
Low energy/tired	Yes	No	
Not sleeping well	Yes	No	
Poor feeding/poor appetite	Yes	No	
Feeling sick	Yes	No	N/A
Vomiting	Yes	No	
Diarrhoea	Yes	No	
Constipation	Yes	No	
Abdominal pain/ tummy ache	Yes	No	N/A
Colic/grimacing/pulling up legs	Yes	No	N/A
Muscle aches or pains	Yes	No	N/A
Increased urinary frequency or number of wet nappies	Yes	No	
Smelly urine	Yes	No	
Dark or cloudy urine	Yes	No	
Pain/crying on passing urine	Yes	No	
Day or bed wetting when previously dry	Yes	No	
Poor weight gain	Yes	No	

Other information about this illness:
Since the visit to your GP/Nurse when you agreed for your child to take part in the study, has your child:

Been admitted to hospital	Yes	No	
If yes, date of admission:	Day:	Month:	Year:
If yes, how many nights did your child spend in hospital?			

Since the visit to your GP/Nurse when you agreed for your child to take part in the study, have you contacted (but not visited) any of the following about your child's illness:

GP in usual working hours	No	Yes	If yes, how many times?	
Nurse in usual working hours	No	Yes	If yes, how many times?	
Hospital A&E or 'Casualty' department	No	Yes	If yes, how many times?	
Out of Hours GP service	No	Yes	If yes, how many times?	
Pharmacist	No	Yes	If yes, how many times?	
NHS Direct	No	Yes	If yes, how many times?	
Specialist	No	Yes	If yes, how many times?	
Other	No	Yes	If yes, how many times?	
	If yes, please specify:			

Since the visit to your GP/Nurse when you agreed for your child to take part in the study, have you taken your child to visit any of the following about this illness:

GP in usual working hours	No	Yes	If yes, how many times?	
Nurse in usual working hours	No	Yes	If yes, how many times?	
Hospital emergency department	No	Yes	If yes, how many times?	
Out of Hours GP service	No	Yes	If yes, how many times?	
Pharmacist	No	Yes	If yes, how many times?	
Walk in centre	No	Yes	If yes, how many times?	
Specialist	No	Yes	If yes, how many times?	
Other	No	Yes	If yes, how many times?	
	If yes, please specify:			

What method was used to obtain a urine sample?

How easy was it to obtain a urine sample in this way (from 0-5 with 0 very difficult and 5 very easy) _____

Background

Does your child who is participating in this study attend or have any of the following?

School	Yes	No
Nursery or day care	Yes	No
If yes, is any food provided for your child?	Yes	No
Child minder	Yes	No
Breakfast club	Yes	No

How many days if any have you or anyone else had to take off work because of your child's illness?

Occupation of person who had to take most time off?

In the 3 months before this illness, has your child had any other illnesses?	Yes	No

If yes, please specify:

Approximate date of illness			
Day	Month	Year	Nature of illness

If I can just ask you to think back to when your child was first born,

Appendix 4: Appendices relating to Chapter 4: Method

Appendix 4.1: WORD funding for the study

Appendix 4.2: Ethics committee amendments and poster

Appendix 4.3: Letter of invitation to practices

Appendix 4.4: Summary of study procedures for practices

Appendix 4.5: Recruitment log

Appendix 4.6: Letter of invitation to parents

Appendix 4.7: Parent information sheet

Appendix 4.8: Consent form

Appendix 4.9: CRF section one

Appendix 4.10: CRF section two

Appendix 4.11: CRF section three

Appendix 4.12: Leaflets describing urine sampling methods

Appendix 4.13: Telephone follow up questionnaire

Appendix 4.14: 6 month follow up

Appendix 4.15: Data cleaning and management log

Appendix 4.16: Data cleaning decision rules

Appendix 4.17: STROBE checklist

Appendix 4.1: WORD funding for the study

Wales Office of Research and Development for
Health and Social Care
Swyddfa Cymru ar gyfer Ymchwil a Datblygu
Iechyd a Gofal Cymdeithasol

Llywodraeth Cynulliad Cymru
Welsh Assembly Government

Professor C Butler
Department of Primary Care and Public Health,
Cardiff University,
Neuadd Meirionnydd,
School of Medicine,
Cardiff University, H
Heath Park,

Your ref:
Our ref: WORD/RFS/RCE

Date: 30 November 2007

Dear Professor Butler,

Wales Office for Research and Development for Health and Social Care Research Funding Scheme, (WORD RFS), third call 2007-2008.

Project title: EURICA: The Epidemiology of Urinary Tract Infection (UTI) in Children with Acute Illness in Primary Care

Project reference: H07-3-008

I am delighted to confirm that your application for funding under the WORD Research Funding Scheme has been successful.

The amount awarded is £139,897.

The project is expected to commence 1st April 2008. Payments will be quarterly in arrears. The first payment will include a sum to assist with start-up costs and initial project expenditure. The remainder of the grant will be paid at the intervals indicated in the schedule attached to the Terms and Conditions for the grant.

I would like to emphasise that the grant award is conditional on the project commencing 1 April 2008 or sooner.

Parc Cathays • Cathays Park
Caerdydd • Cardiff
CF10 3NQ

Ffôn • Tel: 029 2082 6435
GTN: 1208 6435
Ffacs • Fax: 029 2082 3997
Ebost • Email: robertedwards@wales.gsi.gov.

Funding will be awarded on the basis of the information given in your application, and any subsequent amendments agreed with WORD prior to the date of this letter. The offer is subject to both you and the University accepting all the non negotiable conditions set out in this letter, the Terms and Conditions and accompanying annexes. Terms and conditions will be forwarded to the University contracts department in the next few days. If you wish to accept the grant offer please confirm by email and arrange for the Terms and Conditions to be signed and returned to me by 31 December 2007.

I wish you every success with the project and if you have any questions relating to the grant conditions please contact me or Andy Privett at WORD.

Yours sincerely,

Robert Edwards
Grant Scheme Manager
Wales Office of Research and Development

Parc Cathays • Cathays Park
Caerdydd • Cardiff
CF10 3NQ

Ffôn • Tel: 029 2082 6435
GTN: 1208 6435
Ffacs • Fax: 029 2082 3997
Ebost • Email: robertedwards@wales.gsi.gov.

Appendix 4.2: Ethics committee amendments and poster

- Is your child under 5 years old?
- Is your child unwell?
- Has your child been ill for less than 28 days?

Your child may be eligible for the EURICA research study

When young children are unwell, sometimes the cause is a water (urine) infection, even without any specific symptoms. Urine infections can therefore be hard to detect in young children.

This important research study will help us to understand urine infections in children and how to detect them as early as possible.

Please ask at reception for further information

This study involves answering some questions about your child's illness and sending a urine sample to see if there could be a urine infection causing their symptoms.

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

EURICA

South East Wales Trials Unit
Uned Ymchwil De-ddwyrain Cymru
sewtu

Version 1 19/11/08

Canolfan Gwasanaethau Busnes
Business Services Centre

South East Wales Research Ethics Committee Panel C
Direct Line: 02920 376823/376822
Fax: 02920 376835
E-mail: Carl.phillips@bsc.wales.nhs.uk

Professor Christopher Butler
Head of the Department of Primary Care & Public Health
Department of Primary Care & Public Health
Cardiff University
Neuadd Meirionnydd, Heath Park
CF14 4XN

27 November 2008

Dear Professor Butler

Study title:	**EURICA: The Epidemiology of Urinary Tract Infection (UTI) in children with acute illness in primary care**
REC reference:	**08/WSE03/11**
Amendment number:	**1**
Amendment date:	**19 November 2008**

Thank you for submitting the above amendment, which was received on 26 November 2008. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	1	19 November 2008
Advertisement	1 (Poster)	19 November 2008

Notification of the Committee's decision

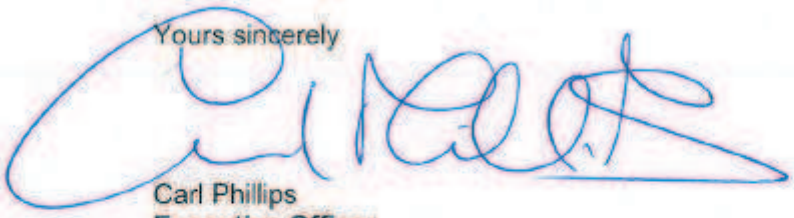
The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

08/WSE03/11: Please quote this number on all correspondence

Yours sincerely



Carl Phillips
Executive Officer
South East Wales Research Ethics Committees

Copy to: R&D Department for Cardiff University

R&D Department for Cardiff & Vale NHS Trust

Canolfan Gwasanaethau Busnes
Business Services Centre

South East Wales Research Ethics Committee Panel C

Direct Line: 02920 376823/376822
Fax: 02920 376835

22 December 2008

Professor Christopher Butler
Head of the Department of Primary Care & Public Health
Department of Primary Care & Public Health
Cardiff University
Neuadd Meirionnydd, Heath Park
CF14 4XN

Dear Professor Butler

Study title:	**EURICA: The Epidemiology of Urinary Tract Infection (UTI) in children with acute illness in primary care**
REC reference:	**08/WSE03/11**
Amendment number:	**1**
Amendment date:	**19 November 2008**

The above amendment was reviewed at the meeting of the Sub-Committee of the South East Wales REC held on 17 December 2008.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	1	19 November 2008
Advertisement	1 (Poster)	19 November 2008

Canolfan Gwasanaethau Busnes
Ty Churchill
17 Ffordd Churchill
Caerdydd, CF10 2TW
Ffôn: 029 20 376820 WHTN: 1809
Ffacs: 029 20 376826

Business Services Centre
Churchill House
17 Churchill Way
Cardiff, CF10 2TW
Telephone: 029 20 376820 WHTN: 1809
Fax: 029 20 376826

NHS WALES GIG CYMRU
rhan o Addysgu Bwrdd Iechyd Lleol Powys / part of Powys Teaching Local Health Board

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/WSE03/11:	**Please quote this number on all correspondence**

Yours sincerely

Mrs Jagjit Sidhu
Committee Co-ordinator

E-mail: jagit.sidhu@bsc.wales.nhs.uk

Enclosures — List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: *Dr K J Pittard Davies,*

South East Wales Research Ethics Committee Panel C

Attendance at Sub-Committee of the REC meeting on 17 December 2008

Name	*Profession*	*Capacity*
Mrs J Darmanin	Nurse	Expert
Mrs J Jenkins	Chair and Lay Member	Lay

Appendix 4.3: Letter of invitation to practices

Department of Primary Care & Public Health
Cardiff University
School of Medicine
Neuadd Meirionnydd
Heath Park
Cardiff CF14 4XN
Tel +44(0)29 2068 7174
Fax +44(0)29 2068 7612

Dear

Re: EURICA: The Epidemiology of Urinary Tract Infection (UTI) in Children with Acute Illness in Primary Care

We are writing to ask for your practice's help with our research study which aims to answer an important research question for primary care clinicians.

We want to find out how common UTI is in ill children presenting in primary care.

This is important because:

1) UTI in young children has been associated with long-term complications including renal scarring, renal failure and hypertension. Early recognition and treatment of UTI in children is thought to reduce this risk.

2) UTI in children is often missed in primary care because the symptoms are non-specific. One UK study found that 50% cases of UTI were missed in children.

3) NICE have recently published a guideline concerning UTI in children. This emphasises prompt diagnosis and treatment of UTI in children, and promotes a high level of suspicion, with increased urine sampling in young children with non-specific symptoms.

4) We currently do not know how common UTI is in acutely ill children presenting in primary care because no other studies have systematically sampled urine from this population. We need to know this in order to determine whether UTIs in children really are being missed and to inform decisions about sampling, diagnosis and management.

We would like you to recruit children under the age of five who present with an acute illness (≤28 days); take their consent, complete a brief form (CRF) and collect a urine sample. Most of this can be completed by a nurse or health care assistant.

Children should then be managed in the normal way. This is an observational study. We are not asking you to change your clinical management of children; children will not be randomised, will not receive additional/experimental medication and there are no blood tests. Consent will allow researchers to access to patients' medical notes, urine results, and for a follow-up telephone call at 2 weeks.

We will reimburse you for your time in participating in this study.

Department of Primary Care & Public Health
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Neuadd Meirionnydd
Heath Park
Cardiff CF14 4XN
Tel +44(0)29 2068 7174
Fax +44(0)29 2068 7612

If you agree to help us to recruit patients, **we will pay you £45 for every child** you recruit with a completed CRF & urine sample (if you recruit 100 children, this will mean a payment of £4500). We will also provide equipment for urine collection, dipsticks, and thermometers. A Consultant Paediatric Nephrologist will be available for any clinical advice should you need it during the study.

The study is being funded by the Welsh Assembly Government. It has been approved by the South East Wales Local Research Ethics Committee. The study is being supported by the South East Wales Trials Unit and in collaboration with CRC-Cymru.

We hope that you will be able to help us with this important research. We will contact you or your practice manager by telephone shortly to discuss the study and answer any questions. For further information please don't hesitate to contact us.

Thank you for your time.
Yours sincerely,

Dr. Kathy O'Brien
Study Manager
Primary Care & Public Health
Cardiff University
Telephone: 029 2068 7174
Email: obrienka@cf.ac.uk

Mandy Iles
Study Administrator
Primary Care & Public Health
Cardiff University
Telephone: 029 20687191
Email: ilesaj1@cf.ac.uk

Professor Christopher Butler
Head of Department of Primary Care & Public Health
Cardiff University
Telephone: 029 2068 7168

Appendix 4.4: Summary of study procedures for practices

SUMMARY OF DOCUMENTS & SAMPLES

STUDY DOCUMENTS

1) Complete screening log for all eligible children both recruited and not recruited. This should be faxed to Kathy O'Brien at Cardiff University 029 2068 7612 each week.
2) For those consented, give the carbon copy of the signed consent form to the carer to keep.
3) Fax consent form and white section 1 – patient registration form to Kathy O'Brien at Cardiff University 029 2068 7612
4) Keep original consent form & section 1 in the site file.
5) Ensure yellow section 2 and orange section 3 have been completed and keep these in the site file for copying and collection by CRC-Cymru on a monthly basis.

URINE SAMPLE COLLECTION & LABELLING

1) Try and obtain a urine sample whilst the child is in the surgery.
2) Urine samples should be collected by clean catch method as first choice or by the use of a Newcastle collection pad in the nappy.
3) Urine should then be transferred into a white topped universal container.
4) The sample should be labelled with the child's name, address and date of birth AND with a red EURICA label with the patient ID number on. PLEASE CHECK THIS MATCHES THE CRF & PATIENT DETAILS.
5) The sample should be tested with a dipstick and results recorded in the yellow section 2 of the CRF.
6) A standard microbiology form should be completed as normal with the child's full details on AND a red EURICA label on all pages of the form.
7) The urine sample should be refrigerated until collection.

WHEN A URINE SAMPLE IS NOT OBTAINED IN SURGERY

1) Ensure carers know how to obtain the urine sample and have been given both verbal and written instructions.
2) Ensure carers have been given the necessary equipment, a white topped universal collection container labelled with patient details AND a red EURICA label, and a microbiology form labelled with patient details AND a red EURICA label on each page.
3) Please emphasise the importance of the urine sample, not just for the research study but for diagnosing unrecognised UTI in children.
4) Record the carer's contact details and ring the next morning to remind them to return the urine sample.

Appendix 4.5: Recruitment log

South East Wales Trials Unit
Uned Ymchwil De-ddwyrain Cymru

EURICA SCREENING LOG – Please fax weekly to Kathy O'Brien Fax no: 029 2068 7612

GP Surgery Name: _____Centre Identifier (CID)

0	9

For all children aged before their 5th birthday who consult, please check their eligibility for EURICA. Complete this table every time you consider a patient for EURICA.

Date of consultation	Patient's date of birth	Patient's gender M/F	Was patient recruited?	If recruited please give Patient's Study Number	If recruited, has urine sample been collected?	If not recruited please give reason for exclusion/not consented/not approached?

Department of Primary care & Public Health
Head of Department Professor Christopher Butler

Adran Gofal Cynradd a Iechyd y Cyhoedd
Pennaeth Adran Yr Athro Christopher Butler

Appendix 4.6: Letter of invitation to parents

Department of Primary Care & Public Health
Cardiff University
Centre for Health Sciences Research
School of Medicine
Neuadd Meirionnydd
Heath Park
Cardiff CF14 4XN
Tel Ffon +44 (0)2920687174
Fax Facs +44 (0)2920687612

Adran Gofal Cynradd a Iechyd y Cyhoedd
Prifysgol Caerdydd
Canolfan Ymchwil Gwyddoriaeth Iechyd Yr Ysgol Feddygol
Neuadd Meirionnydd
Parc y Mynydd Bychan
Caerdydd CF14 4XN

EURICA: The Epidemiology of Urinary Tract Infection (UTI) in Children with Acute illness in Primary Care

Letter to Parent/Carer

I am writing to ask if you will help us with our research. We are conducting a study to find out how common urine infections are in children under the age of five who visit their doctor with an illness. This may be any illness, including coughs and colds – there may not be any obvious signs of a urine infection. Asking you to help with our research does not mean that we think your child has a urine infection.

As young children often do not have any obvious signs of a urine infection, it can be hard for doctors to identify which children have urine infections. We will see how many ill children actually do have a urine infection by sending a urine sample for all children. We hope to improve understanding and diagnosis of urine infections in children. It is important to identify a urine infection if it is present, as there is treatment available to treat this, and early treatment may avoid complications later on.

If you agree to help us with this research, the nurse, GP or health care assistant will take some details about your child's illness, check your child's temperature and collect a urine sample. Your child will then be treated as normal by your doctor. All information collected about you or your child during the course of the research will be kept strictly confidential.

Please find enclosed a patient information sheet explaining the study in more detail. Your GP, Nurse or Health Care Assistant will be able to answer any other questions you have.

Thank you for your interest. We hope that you will help us with our research, but if you are not able to do so, this will not adversely affect yours or your child's care in any way.

Yours sincerely,

Dr. Kathy O'Brien

Email:obrienka@cf.ac.uk Telephone: 029 2068 7174 or 029 2068 7191

1st February 2008 Version 1

Appendix 4.7: Parent information sheet

South East Wales Trials Unit

Uned Ymchwil De-ddwyrain Cymru

EURICA: The **E**pidemiology of **Ur**inary Tract **I**nfection (UTI) in **C**hildren with **A**cute illness in Primary Care
Parent/Carer Information Sheet

We would like to invite you and your child to take part in a research study. Before you decide, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 of the information sheet

Study title

EURICA: The Epidemiology of Urinary Tract Infection (UTI) in Children with Acute illness in Primary Care

(Protocol Version 4, 24/07/2009)

What is the purpose of this study?

Bladder or urinary tract infections in children are common. Diagnosing them is important because effective treatment can be given. In some cases these infections may lead to long term medical problems which could be prevented by early treatment. This may be a particular problem in young children under the age of five.

We do not know how many children, under the age of five, have urinary tract infections. We do know that infection is more common in children who are unwell. It may be important for GPs (General Practitioners) and nurses to check the urine of *all* children under the age of five who are unwell, even if there seems to be another reason for the illness. Sometimes children have urine infections even if they do not complain about problems with passing urine. However, unless we know how common these infections really are, we will not be able to give proper guidance to GPs and nurses about this.

We are interested in finding out how many ill children who come to see their GP or nurse actually have a urinary tract infection. To do this, we need to get urine samples from large numbers of ill children. We also want to see whether a test on the urine, which can be completed in the GP surgery, is accurate. We also hope to identify some symptoms that may help diagnose urinary tract infections, and to try

and understand what might cause infections with bacteria that are not killed by the usual antibiotics.

Why have we been invited?

We are asking GP surgeries in Wales to help us with this research and we hope to include 1600 children in this study. You have been chosen simply because your child is unwell and is under the age of five (aged before their fifth birthday). Asking you to help with this research does *not* mean we believe your child has a urine infection. We are simply doing a check of the urine and gathering additional information that might not otherwise have been done.

Do we have to take part?

It is up to you to decide whether or not you want your child to take part. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you or your child receives now or in the future.

What will happen to my child if he/she takes part?

Firstly, the nurse or health care assistant or doctor will ask you about the symptoms that your child has had and will check your child's temperature, breathing rate and heart rate. You will then be helped to obtain a urine sample from your child. In most cases, you will be given a sterile pot to collect the sample in. If this is difficult, particularly in children under the age of 2, the nurse will give you a pad to put in the child's nappy to collect the urine sample, and you will be shown how to do this.

The urine sample will be tested with a test strip in the surgery, and then sent to the hospital laboratory. Your child will then be examined by the doctor or nurse, who will decide on treatment as normal.

We will try to obtain a urine sample before you leave the surgery, although in some instances it may be necessary to get you to drop the sample off later.

Taking part in the study will mean spending a little more time in the surgery for the nurse to ask about symptoms and to collect the urine sample. It may involve up to an additional 15-30 minutes of your time at the surgery. However in most cases the nurse will see you whilst you are waiting to see the doctor.

At the laboratory, routine tests will be performed on your child's urine sample, to see if a bacterial infection is present, and if so, which antibiotics would be the best treatment for this particular infection. These routine test results will be sent to your GP as normal, who will then decide if your child needs to receive any treatment or further investigations. These test results will also be available to the research team.

In addition, further laboratory tests will be performed on the urine sample. These tests will help us to understand more about the bacteria which cause urinary tract

infections, and how the body responds to these infections. Although these tests will not directly be of benefit to your child, they will improve our understanding of urinary tract infections in children, and help with the diagnosis and treatment of this important condition in the future. Your child's urine may be stored for up to five years for additional laboratory tests for research purposes, concerning urinary tract infection.

Your consent will allow researchers to access your child's notes (up to 6 months after your child's initial visit to the doctor) and to look at the results of any tests. This may include GP out of hours, Accident & Emergency and hospital notes as well as GP notes. It will also allow us to telephone you approximately two weeks later to ask some questions about how your child is feeling and what treatment (if any) they have received. We will also ask some questions about illnesses and antibiotic treatments of other family members to help work out whether any other factors contribute to these infections. However you do not have to answer all of the questions if you do not want to. We won't be contacting everyone who takes part by telephone. In general we will only telephone those whose urine result showed an infection or in those where the result was unclear and the urine sample needed to be repeated.

What if my child's urine sample shows an infection?

In some cases a repeat urine sample may be needed to confirm the result. If your child turns out to have a urine infection, your doctor will inform you of the result and arrange any treatment or follow up if this is necessary.
We will also request two further urine samples from your child, one and two weeks later. These will be sent to the laboratory for routine tests to check that the infection has cleared, and additional tests will be performed (as before) to help further understanding of urinary tract infections in children. The urine may be stored for up to five years for additional laboratory tests. One of the research team will contact you by telephone 2 weeks after your initial visit to the doctor as described above.

What if my child's urine sample is negative (no infection)?

No further urine samples will usually be needed, and you will not be contacted by telephone. However, we will be asking for a repeat urine sample in a small number of children even if the initial result is negative. If your child is still unwell or you are worried about your child you should contact your doctor in the normal way.

What are the possible disadvantages and risks of taking part?

Taking part will mean that we take up a little of your time asking certain questions about your child's illness, and in taking a urine sample that may not otherwise have been taken. Taking a urine sample in this way is safe and does not cause discomfort. We will not take any blood as part of this research study.

If your child is found to have an infection in the urine, another urine test may be necessary, as might a visit to the hospital for possible further tests. Most children found to have infected urine will have an ultrasound scan of their kidneys - this is not painful or invasive. Treatment and further tests will only be performed if your doctor,

or a hospital specialist, feels your child needs them. They will not be performed as part of this research study.

What are the possible benefits of taking part?

It is possible that there may be no direct benefit to your child taking part, however if your child is found to have an infection, treatment can be given. Improving the understanding, diagnosis and management of urinary tract infections may benefit your own child or other children in the future.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you and your child will be handled in confidence. The details are included in Part 2.

This completes Part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2 of the information sheet

What if relevant new information becomes available?

Sometimes we get new information about the condition being studied in a research study. If this happens, the research team will inform your doctor. Your doctor will tell you and discuss with you whether you and your child should continue with the study. If you decide not to carry on, this will not affect the care of you or your child in any way.

If the study is stopped for any other reason, we will tell you and the care of you and your child will continue as normal.

What will happen if I don't want to carry on with the study?

You and your child can withdraw from the study at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you or your child receives now or in the future.
If you do decide to withdraw from the study, we will use the data collected up to your withdrawal but will collect no further data or samples for research purposes. Any urine samples which are not needed for your child's care, and which can still be identified as your child's will be destroyed if you wish.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you can speak to the researchers at Cardiff University who will do their best to answer your questions (contact details below).

Contact for further information about the study

Dr Kathy O'Brien,
Department of Primary Care & Public Health
Cardiff University
Neuadd Meirionnydd
Heath Park
Cardiff
CF14 4XN

Tel. 029 2068 7174
or 029 2068 7191

If you remain unhappy and wish to complain formally, you can do this through the Research and Commercial Division of Cardiff University (details below).

Contact for formal complaints procedure at Cardiff University

Chris Shaw
Research Governance Officer
Cardiff University
Research And Commercial Division
30-36 Newport Road
Cardiff
CF24 0DE

Tel. 029 2087 9130
or 029 2087 9277

Harm

In the event that something does go wrong and you or your child are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cardiff University but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?

Yes. All information which is collected about your child during the course of the research will be kept strictly confidential. Study data stored at the University will be kept separate from personal information (names and addresses). Only authorised persons on the research team will have access to view identifiable data. However, in some instances authorised persons from regulatory authorities may need to access data for monitoring of the quality of the research. All members of the research team and regulatory bodies are trained in data protection issues and bound by the terms of the Data Protection Act 1998.

Once the study is complete and it is no longer necessary to keep identifiable information or contact details, we will destroy our records of this personal information. Fully anonymised data records will be kept securely for 15 years in line with Cardiff University's policies.

Your child's urine may be stored securely for up to five years for further research concerning urine infections. Names and addresses will be removed from all urine samples stored for research purposes. Further ethical approval will be sought from the Ethics committee for any further research on these urine samples.

Involvement of the General Practitioner

As your Doctor is involved in helping us with this research study, he or she will be aware of your child's involvement in the study if you decide to help us.

What will happen to any samples I give?

Urine samples will be obtained from your child (as described in part 1) and sent to the routine laboratory to see if there is a urine infection or not. These tests are often part of normal clinical practice for ill children, although they are not necessarily performed on all ill children. After these routine urine tests have been completed, the urine will have further tests for research purposes (as described in part 1). For the routine tests, the urine samples need to be clearly labelled with your child's name, address and date of birth so that the results can be reported back to your doctor. Once these routine tests are completed, names and addresses will be removed from the samples prior to the further, research-related tests.

Will any genetic tests by done?

No. We will not be doing any tests on human DNA.

What will happen to the results of the research study?

A report of the research results will be completed and submitted to the Welsh Assembly Government who are funding the study. Results will also be published in scientific journals and presented at scientific conferences. Your child will not be identified in any report, publication or presentation; all results will be completely anonymous.

Once the research study is completed, if you would like a report of the research findings this will be available by contacting Dr Kathy O'Brien (see below).

Who is organising and funding the research?

This study is being organised by the Department of Primary Care and Public Health, Cardiff University with the help of your doctor's surgery. The research is being funded by the Welsh Assembly Government.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the South East Wales Research Ethics Committee.

Contact for Further Information

Dr Kathy O'Brien,
Department of Primary Care & Public Health , Cardiff University,
Neuadd Meirionnydd, Heath Park, Cardiff. CF14 4XN

Tel. 029 2068 7174
or 029 2068 7191

THANK YOU FOR CONSIDERING TAKING PART IN THE STUDY.

7th September 2009 Version 3

Department of Primary Care & Public
Cardiff University
Centre for Health Sciences Research
School of Medicine
Neuadd Meirionnydd
Heath Park
Cardiff CF14 4XN
Tel +44 (0)2920687174
Fax +44 (0)2920687612

Adran Gofal Cynradd a Iechyd y Cyho
Prifysgol Caerdydd
Canolfan Ymchwil Gwyddoriaeth Iech
Ysgol Feddygol
Neuadd Meirionnydd
Parc y Mynydd Bychan
Caerdydd CF14 4XN

Centre Identification Number:
Patient Identification Number for this study

CONSENT FORM

Title of Project:
EURICA: The Epidemiology of Urinary Tract Infection (UTI) in Children with Acute illness in Primary Care
(Protocol Version 4 dated 24/07/09)

Name of Researcher: Dr Kathy O'Brien

Please initial box

1. I confirm that I have read and understood the information sheet dated 7th September 2009 (Version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without mine or my child's medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's medical notes and data collected during the study, may be looked at by the research team from Cardiff University, from regulatory authorities or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records. ☐

4. I understand that my child's urine will be tested by the laboratory in the normal way and have additional exploratory laboratory tests performed. It may be stored for up to five years for research concerning urinary infections. ☐

5. I agree for my child to take part in the above study. ☐

_____
Name of Child (please print)

_____	_____	_____
Name of Parent/Carer (please print)	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for carer/parent; 1 for researcher site file; 1 (original) to be kept in medical notes
5th February 2010 Version 3

Appendix 4.9: CRF section one

Draft

EURICA

CID ☐☐ PID ☐☐☐☐

EURICA: The Epidemiology of Urinary Tract Infection in Children with Acute Illness in Primary Care

Section 1: Patient Registration Form

Inclusion criteria

Please include child if the answer is 'yes' to all of the following:

Q1	Aged less than 5 years (before fifth birthday)	☐	Yes	☐	No
Q2	Acute Illness for less than or equal to 28 days	☐	Yes	☐	No
Q3	First time in this study	☐	Yes	☐	No
Q4	Written consent from parent or carer to participate	☐	Yes	☐	No

Exclusion Criteria

Please exclude if you answer 'Yes' to any of the following:

Q5	Taking regular long term antibiotics (daily for past 28 days or more)	☐	Yes	☐	No
Q6	On chemotherapy	☐	Yes	☐	No
Q7	Currently taking oral or intramuscular steroids greater than or equal to 10mg of prednisolone per day (or equivalent) for greater than or equal to two weeks Note: Inhaled steroids are NOT an exclusion criteria.	☐	Yes	☐	No

If the patient satisfies all eligibility and exclusion criteria please continue to the next section

Draft

EURICA

CID PID

EURICA: The Epidemiology of Urinary Tract Infection in Children with Acute Illness in Primary Care

Patient Registration Form

Date of consultation D D / M M / Y Y

Child's details

Q8 First Name

Q9 Surname

Q10 Date of Birth D D / M M / Y Y

Q11 Gender ☐ Female ☐ Male

Carer details

Q12 First Name

Q13 Surname

Q14 Relationship to child ☐ Mother ☐ Father ☐ Other please specify:

Q15 House Number/Name & Street Address

Q16 Town

Q17 City

Q18 Postcode –

Q19 Contact Telephone Number

Q20 Mobile Number

Appendix 4.10: CRF section two

Draft

EURICA

CID PID

Section 2: Case Record Form

Nurse/Healthcare Assistant to ask parent/carer

Q21 Date of onset of illness ☐☐ / ☐☐ / ☐☐

Patient's Symptoms

Q22	Runny or blocked nose	☐ Yes	☐ No	
Q23	Sore throat	☐ Yes	☐ No	
Q24	Earache or holding ear	☐ Yes	☐ No	
Q25	Cough	☐ Yes	☐ No	
Q26	Difficulty breathing	☐ Yes	☐ No	
Q27	Hot/feverish	☐ Yes	☐ No	
Q28	Rash	☐ Yes	☐ No	
Q29	Irritable/grouchy	☐ Yes	☐ No	
Q30	Clinginess/needing extra care	☐ Yes	☐ No	
Q31	Low energy/tired or lost interest in playing	☐ Yes	☐ No	
Q32	Poorer sleep	☐ Yes	☐ No	
Q33	Muscle aches or pains	☐ Yes	☐ No	☐ N/A
Q34	Poorer feeding/poorer appetite	☐ Yes	☐ No	
Q35	Diarrhoea	☐ Yes	☐ No	
Q36	Constipation now	☐ Yes	☐ No	
Q37	Constipation in the past	☐ Yes	☐ No	
Q38	Vomiting	☐ Yes	☐ No	
Q39	Nausea	☐ Yes	☐ No	☐ N/A
Q40	Abdominal pain/tummy ache	☐ Yes	☐ No	☐ N/A
Q41	Colic/grimacing/pulling up legs	☐ Yes	☐ No	☐ N/A
Q42	Bed wetting/clothes wet when previously dry	☐ Yes	☐ No	☐ N/A
Q43	Smelly urine	☐ Yes	☐ No	
Q44	Dark or cloudy urine	☐ Yes	☐ No	
Q45	Pain/crying on passing urine	☐ Yes	☐ No	
Q46	Blood in urine	☐ Yes	☐ No	
Q47	Poor urine flow (interrupted or intermittent)	☐ Yes	☐ No	
Q48	Increased urinary frequency or number of wet nappies	☐ Yes	☐ No	
Q49	Poor weight gain/weight loss	☐ Yes	☐ No	
Q50	Were there any other symptoms?	☐ Yes	☐ No	

If **YES**, please list in the space provided.

Section 2: Case Record Form

Nurse/Healthcare Assistant to ask parent/carer

Q51 Was the child's temperature measured (by the parent/carer) at any time during this illness, prior to visiting the GP? ☐ Yes ☐ No

If **YES**, what was the highest temperature recorded by the parent/carer ☐☐.☐ °C

Q52 Please ask the parent/carer to tick a box from 0 to 4 of how unwell they feel their child is today. 0 is not unwell and 4 is severely unwell.

☐ **Normal/not unwell** ☐ **Slightly unwell** ☐ **Moderately unwell** ☐ **Very unwell** ☐ **Severely unwell (as bad as it could be)**

Q53 Has the child had any medications containing **paracetamol** (e.g calpol) for this illness? ☐ Yes ☐ No

If YES please give details starting with the most recent dose

	Name of medication	**Date** (D D / M M / Y Y)	**Approximate time**
Most recent dose	☐☐☐☐☐☐☐☐☐☐	☐☐ / ☐☐ / ☐☐	☐☐ : ☐☐

Q54 Has the child had any medications containing **ibuprofen** (e.g nurofen, cuprofen or calprofen) for this illness? ☐ Yes ☐ No

If YES please give details starting with the most recent dose

	Name of medication	**Date** (D D / M M / Y Y)	**Approximate time**
Most recent dose	☐☐☐☐☐☐☐☐☐☐	☐☐ / ☐☐ / ☐☐	☐☐ : ☐☐

Background Information

These questions relate to other medical problems that the child has or has had in the past.

Q55 Has the child ever been diagnosed with a UTI before ☐ Yes ☐ No

If YES please give approximate dates, with most recent first

☐☐ / ☐☐ / ☐☐ (D D / M M / Y Y)

☐☐ / ☐☐ / ☐☐ (D D / M M / Y Y)

Has the child ever been diagnosed with any of the following?

Q56	Asthma	☐ Yes	☐ No	☐ Don't Know
Q57	Diabetes	☐ Yes	☐ No	☐ Don't Know
Q58	Eczema	☐ Yes	☐ No	☐ Don't Know
Q59	High blood pressure	☐ Yes	☐ No	☐ Don't Know

Section 2: Case Record Form

Nurse/Healthcare Assistant to ask parent/carer

Q60 Kidney or bladder disease ☐ Yes ☐ No ☐ Don't Know

If **YES** please give name of kidney or bladder disease

Q61 Has the child had illnesses in the past with a high temperature but no obvious cause or diagnosis? ☐ Yes ☐ No ☐ Don't Know

Q62 Any other illnesses ☐ Yes ☐ No ☐ Don't Know

If **YES** please specify

Please explain to the parent/carer that the next set of questions relate to the child's birth and early life. There are also some questions concerning the pregnancy of the child.

We are asking these questions because it is thought that these early experiences may influence the chance of developing a urine infection or may affect the way the body deals with infection later on in childhood.

We recognise that these questions are more personal and they do not need to answer them if they would rather not.

Q63 Approximately how many weeks did the pregnancy last? (40 weeks is full term)

Q64 Was the child ever breast fed? ☐ Yes ☐ No

Months Days

Q65 If YES, for how long were they fed only human breast milk?

Q66 Were any antibiotics taken by the mother during pregnancy? ☐ Yes ☐ No ☐ Don't Know
If YES please specify:

Name of antibiotic 1

Name of antibiotic 2

Q67 Were there any abnormalities of the child's kidneys, bladder or ureters on antenatal ultrasound scans? ☐ Yes ☐ No ☐ Don't Know

Please specify if known:

Section 2: Case Record Form

Nurse/Healthcare Assistant to ask parent/carer

Q68 **Only** if the child is a boy please ask:

Has the child been circumcised? ☐ Yes ☐ No

Family History

The next set of questions relate to close family members of the child this includes mother, father and any brothers or sisters who are blood relatives of the child. We are asking these questions to see whether urine infections run in families.

Q69 Has the child's parents, brothers or sisters ever been diagnosed with a urinary tract infection (UTI) during childhood (under 16)? ☐ Yes ☐ No ☐ Don't Know

	Relative 1	Relative 2	Relative 3
Relationship to child			
Age of first UTI			
Number of episodes of UTI			

Q70 Has the child's parents, brothers or sisters ever been diagnosed with a kidney or bladder problem? ☐ Yes ☐ No ☐ Don't Know

	Relative 1	Relative 2
Relationship to child		
Nature of problem if known		

Examination

Q71 Temperature (using infrared digital thermometer in ear) ☐☐.☐ °C

Q72 Pulse rate ☐☐☐ /min

Q73 Respiratory rate ☐☐ /min

Section 2: Case Record Form

Nurse/Healthcare Assistant to ask parent/carer

Urine Collection

Q74 Was a urine sample collected before leaving the surgery? ☐ Yes ☐ No

Q75 Method of urine sampling used or given to parents ☐ Clean catch ☐ Nappy pad

Q76 Date sample collected ☐☐ / ☐☐ / ☐☐
D D M M Y Y

Q77 Time sample collected (24 HR clock) ☐☐ : ☐☐
e.g 1 3 : 4 5

Q78 Urine Dipstick

Please indicate with a tick if any of the following are present

Leukocytes	☐ Yes	☐ No
Nitrites	☐ Yes	☐ No
Protein	☐ Yes	☐ No
Blood	☐ Yes	☐ No
Ketones	☐ Yes	☐ No
Glucose	☐ Yes	☐ No

Please ensure that the urine sample and both parts of the microbiology form have all patient details and a EURICA label. Please also stick one label here when this is done.

EURICA Label

Appendix 4.11: CRF section three

Draft

EURICA

CID PID

Section 3: Case Record Form

Clinician to complete

Examination

Q79 Ears

☐ Examined ☐ Not Examined → Please go to Q80

Left Ear

☐ Normal

☐ Abnormal

Please tick all that apply

☐ Eardrum red or inflamed
☐ Ear canal red or inflamed
☐ Discharge or blood seen

Right Ear

☐ Normal

☐ Abnormal

Please tick all that apply

☐ Eardrum red or inflamed
☐ Ear canal red or inflamed
☐ Discharge or blood seen

Q80 Throat

☐ Examined ☐ Not Examined → Please go to Q81

If examined please tick all the apply

☐ Normal ☐ Red or inflamed ☐ Swollen or enlarged tonsils ☐ Discharge or pus

Q81 Chest

☐ Examined ☐ Not Examined → Please go to Q82

If examined please tick all that apply

☐ Normal ☐ Wheeze ☐ Crackles

☐ Using accessory muscles ☐ Intercostal or subcostal recession

Q82 Abdomen

☐ Examined ☐ Not Examined → Please go to Q83

If examined please tick all that apply

☐ Normal ☐ Loin tenderness ☐ Enlarged bladder ☐ Mass ☐ Other, please specify

Section 3: Case Record Form

Q83 **General/Overall**

Rash	☐ Yes	☐ No
Dehydrated	☐ Yes	☐ No
Jaundice	☐ Yes	☐ No
Spinal lesion	☐ Yes	☐ No
Other	☐ Yes	☐ No

Please specify

Q84 **Fontanelles**

☐ N/A ☐ Normal ☐ Sunken ☐ Bulging

Q85 Please rate your overall impression of the child by ticking a box

☐ **Normal/not unwell** ☐ **Slightly unwell** ☐ **Moderately unwell** ☐ **Very unwell** ☐ **Severely unwell (as bad as it could be)**

Q86 What is your working diagnosis?

Management at this consultation

Q87 Same day hospital referral? ☐ Yes ☐ No

Q88 Hospital referral but not same day ☐ Yes ☐ No

Q89 Did you prescribe any medication, including antibiotics? ☐ Yes ☐ No

Q90 If yes, please state details

Name of medication 1

Name of medication 2

Name of medication 3

Appendix 4.12: Leaflets describing urine sampling methods

Appendix 4.12: Leaflets describing urine sampling methods

These leaflets are not included in the electronic form of the thesis. Permission was obtained to use them in the study but not explicitly to make them freely available on-line.

Appendix 4.13: Telephone follow up questionnaire

EURICA: The Epidemiology of Urinary Tract Infection in Children with Acute Illness in Primary Care.

Telephone follow-up interview by researcher (at 14 days +/- 3 days after initial consultation)

Name of interviewer:			
Date of interview:	Day:	Month:	Year:

Patient identifiers and contact details

Child's study number		
Child's name	First:	Last:
Carer's name	First:	Last:
Relationship to child		
Telephone number		
Mobile number		

Just to remind you, the day your child saw the doctor was_____
Urine result _____

Symptoms

Would you consider that your child has completely recovered from this illness?	Yes	No

If Yes, how many days did the illness last – from the day you took your child to see the GP/nurse and agreed to take part in this study until complete recovery?

If No, please give details about continuing symptoms:

_____
_____
_____

Other information about this illness:
Since the visit to your GP/Nurse when you agreed for your child to take part in the study, has your child:

Been assessed or admitted to hospital	Yes	No				
If yes, date of admission/assessment:	Day:	Month:	Year:			
If yes, how many nights did your child spend in hospital?	0	1	2	3		
	4	5	6	>6		

Since the visit to your GP/Nurse when you agreed for your child to take part in the study, have you contacted or visited any of the following about your child's illness:

GP in usual working hours	Contacted or visited?	No	Yes	If yes, how many times?	
Nurse in usual working hours		No	Yes	If yes, how many times?	
Hospital A&E or 'Casualty' department		No	Yes	If yes, how many times?	
Out of Hours GP service		No	Yes	If yes, how many times?	
Pharmacist		No	Yes	If yes, how many times?	
NHS Direct		No	Yes	If yes, how many times?	
Specialist		No	Yes	If yes, how many times?	
Other		No	Yes	If yes, how many times?	
		If yes, please specify:			

What method was used to obtain a urine sample?

How easy was it to obtain a urine sample in this way (from 0-5 with 0 very difficult and 5 very easy) _____

Background

Does your child who is participating in this study attend or have any of the following?

School	Yes	No
Nursery or day care	Yes	No
If yes, is any food provided for your child?	Yes	No
Child minder	Yes	No
Breakfast club	Yes	No

Family history

How many other children (aged under 18) live in the same house?						
Please give ages:						

Has anyone in the house (apart from the child in this study) had any illnesses in the past 3 months?

Age of person	Approximate date of illness			
	Day	Month	Year	Nature of illness

Has anyone (children or adults) in the house had antibiotics in the past 3 months?	Yes	No

If yes, please give details:

		Approximate date of antibiotics		
Age of person:	Name of antibiotics:	Day:	Month:	Year:

Does anyone living in the house work in any of the following places:

Hospital	Yes	No
Nursing/care/residential home	Yes	No
GP surgery	Yes	No
School	Yes	No
Other medical or nursing or child care facility	Yes	No

Do you have any other comments about your child's illness or treatment?

_____

Thank you for your help with this study. 01 February 2008 Version 1

Appendix 4.14: Six month follow up

4645

EURICA 6 month follow-up

For each patient who provided a urine sample for the study, we need follow-up data for the 6 month period following recruitment into the study - from the date of recruitment until 6 months later (between the 2 dates below).

Please complete the form below including results of any urine cultures or investigations. If it is easier you can attach a copy of

CID CID **PID** PID **Date of birth** REGDOB

First name REGFIR **Surname** REGSUR

Date of recruitment REGDT **End date for follow-up period** FU6MTHFUDATE

Q1 Number of in-surgery face-to-face consultations (not including routine immunisations & checks) FU1CON

Q2 Number of acute/same day hospital admissions FU2ADM

Q3 Number of out of hours or A+E contacts (including consultations or telephone advice FU3OOH

Q4 Number of courses of oral antibiotics FU4AB

Q5 Number of urine samples sent to the lab FU5UR **Please provide full results below or attach copy**

Q6 Has the child been referred to hospital for any reason during this period? ☐ Yes ☐ No FU6REF

Q7 Has the child been referred for or had any investigations of the urinary tract(bladder, ureters, kidneys) during this period? ☐ Yes ☐ No FU7INV

Q8 If yes, please tick: Ultrasound scan (USS) ☐ FU8SS DMSA scan ☐ FUDMSA
Micturating cystourethrogram (MCUG) ☐ FUMCUG Other ☐ FUOTH

Please provide results of any investigations below or attach copy of results

Date of test or referral	**Name of test or investigation (e.g. urine culture, USS, DMSA,**	**Result - please provide copy of results or full text of results.** Continue over the page if necessary
FUDAT1	FUNAM1	FURES1
FUDAT2	FUNAM2	FURES2
FUDAT3	FUNAM3	FURES3
FUDAT4	FUNAM4	FURES4

Appendix 4.15: Data cleaning and management log

EURICA DATA MANAGEMENT

Database name including version and date	Description
EURICA section 2 v0.0 01.06.2010	Raw data imported from EXCEL for CRF section 2. Some corrections made in EXCEL prior to export.
EURICA section 2 v0.1 01.06.2010	See paper data processing folder. Changes dated 1/6/10 made and saved.
EURICA section 2 v0.2 04.06.2010	See paper data processing folder. Changes dated 4/6/10 made and saved.
EURICA section 2 v0.3 15.06.2010	See paper data processing folder. Changes dated 15/6/10 made and saved
EURICA section 2 v0.4 08.07.2010	See paper data processing folder. Changes dated 8/7/10 made and saved
EURICA section 2 v0.5 15.10.2010	See paper data processing folder. Changes dated 15/10/10 made and saved. CID 08
EURICA URINES v.0.1 16 08 2010	Data checking against paper results. Any errors corrected from: Double data entry checks, Positive/borderline results – checks and entry of repeats – CID 1
EURICA URINES v.0.2 24 08 2010	Data checking against paper results. Any errors corrected from: Double data entry checks, Positive/borderline results – checks and entry of repeats – CID 2, 3, 4, 5, 6
EURICA URINES v.0.3 31 08 2010	Data checking against paper results. Any errors corrected from positive/borderline results – checks and entries of repeats – CID 7, 8, 9, and part of 10.
EURICA URINES v.0.4 20 09 2010	Data checking against paper results. Any errors corrected from positive/borderline results – checks and entries of repeats – 10 completed. Also Mandy's extra file of positive/borderline results which came in later.
EURICA URINES v.0.5 11 10 2010	Data checking against paper results from Mandy's extra file of late consent forms and lab results. CID 8 PID 378 is entered twice so 1 record removed. CID 15 PID 869 entered twice so 1 record removed. Checked against latest Access database & all urine results entered. Mismatch in access database between number with urine results on patient recruitment table and lab results table. All checked against spss and raw data and changes made.

EURICA URINES v.0.6 23 11 2010	Data checking and sorting urines into table. Noted missing values for culture for 6 records and info was present in comments section so entered into culture: 1 1101 Not cultured 4 188 Not cultured 6 1366 Not cultured 6 1369 Not cultured 10 1925 No growth 10 1919 Growth Noted no bacteria for growth>100,000 and in comments states E.coli grown so added to bacteria variable. 10 1919 Escherichia coli 10 2063 Escherichia coli
EURICA URINES v.0.7 10 01 2011	Added urine sample result manually. Sent later by practice. For CID 07 PID 329
Clinician version 0.3 10 01 11.xls located in Teleform, raw data, clinician corrections	See paper data processing folder. Changes for sec 3 CID 01 6-1025 and CID 2 51-94
Clinician version 0.4 11 01 11.xls located in Teleform, raw data, clinician corrections	See paper data processing folder. SEC 3 CID 3 102-135
Clinician Aug 2010 data version 0.1 11 01 11.xls located in Teleform, raw data, clinician corrections	See paper data processing folder. CID 1 1656-1699, 3002,3003
Clinician version 0.5 14 01 11.xls located in Teleform, raw data, clinician corrections	See paper data processing folder. CID 04 156-160, CID 05 202-215
Clinician Aug 2010 data version 0.2 14 01 11.xls located in Teleform, raw data, clinician corrections	NO CHANGES MADE ON 14 01 2011 . CHANGES MADE ON 17 01 11 CID 15 852-883 CID 18 1800-1832
Clinician version 0.6 17 01 11.xls located in Teleform, raw data, clinician corrections	See paper data processing folder CID 6 253-271; 1331-1337 CID 8 352-383 CID 6 273-289 & 1342-1358 CID 7 332-346 CID 5 234-242 CID 9 401-448 CID 10 452-488
DATABASE MERGING	
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\NurseFullSet 310111.sav	Merged all nurse(sec 2) data - R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\SPSS Databases Syntax and Outcomes\EURICA section 2 v.0.6 26.10.2010.sav & - R:\PCAPH\PCAPH\SEWTU

	Studies\EURICA\STATS\TELEFORM\RAW DATA\RAW ORIGINAL DATA\EURICA CRF sec 2 Nurse Aug 2010.xls
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\ClinicianFullSet 310111.sav	Merged all Clinician (sec 3) data - R:\PCAPH\PCAPH\SEWTU Studies\EURICA\STATS\TELEFORM\RAW DATA\Clinician corrections\Clinician Aug 2010 data version 0.2 14 01 11.xls & - R:\PCAPH\PCAPH\SEWTU Studies\EURICA\STATS\TELEFORM\RAW DATA\Clinician corrections\Clinician version 0.6 17 01 11 KO.xls
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\NurseFullSet duplicates removed 070211.sav	Duplicates checked 1 removed and remaining one checked manually with paper CRF any corrections made to R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\NurseFullSet 310111.sav
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\ClinicianFullSetDuplicates removed 070211.sav	Duplicates checked 1 removed and remaining one checked manually with paper CRF any corrections made to R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\ClinicianFullSet 310111.sav
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set)	Combined datasets: R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\ClinicianFullSet 310111.sav & R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\NurseFullSet 310111.sav & EURICA URINES v.0.7 10 01 2011
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) checks 070111	Checks of R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) – and changes made – added CID and PID numbers for REC_IDs 11,3130,3137,6290,8391,8394,8396,9416,9618,9620,11622,15000,61347,91987,91988, 92058
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical	Checks of duplicates and missing ID numbers. See paper copy in data management folder + see related doc. REC_ID 4214 – no PID 214 for CID 4 – should be CID 5. urine result for CID 5 PID 214 matches result exactly so changed to CID 5.

urines (Full set) checks 110111	REC_ID 11: this was accidentally changed from CID 1 PID 1 to CID 20 PID 1 (ie REC_ID 201) between Nursefull set 31 01 11 and Nursefull set duplicates removed 07 02 11. so changed back to CID 1 and Sec 2, 3 and urine results all correctly assigned and checked. All duplicate PID numbers 2050-2080 checked. All urine results correctly assigned.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) checks 140111	Check to see if any have urine dips recorded but no urine results available.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) additional urines 17 02 11	Manually entered additional urine results from NHS path results.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) additional urines 28 02 11	Manually entered additional urine results from NHS path results.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) additional urines 04 03 11	Coded duplicates as 'excluded' Also further checks on duplicate PID numbers. REC_ID9247 should be CID 5 not CID 9 – combined with 5247 and then 9247 deleted. REC_ID 15000 should be CID 9 not CID 1 so combined with 95000 and 15000 deleted. REC_ID 61354 is correct but rest of crf entered as REC_ID 91354 so combined and 91354 deleted. REC_ID 9 and REC_ID 10 – no way of identifying (went back to Access database and they are entered with only this information) so deleted.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\combined nurse clinical urines (Full set) additional urines 07 03 11	After checking with ACCESS and paper CRFs, REC_ID 313 changed to 3137. REC_ID 6347 changed to 61347. REC_ID 11963 changed to 11693. Then start variable checks.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN	Merged with sec 1 from access – table of recruitment Patient recruitment access export recruitment a 07 03 11

ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET (including sec 1) 07 03 2011	
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET additional urines 11 03 2011	Adding additional urine results from Royal Glam and Prince Charles Urine results added for 19 2008 19 2011 19 2019 10 495 10 498 10 1922 10 1923 No consent forms so excluded: 7 323 9 5030 10 2006 5 219 9 416 940274 – no such number. No info in database. No consent form found. Deleted. Added missing gender data Change date variables to namea e.g. dateurineresult becomes dateurineresulta so that I can re-merge access dates.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET 14 03 2011	DOB and Date consultation checks. Consent form checks for those missing this sec 1 info. REC_ID 11963 should be 91963. no info in any section so deleted. Consent forms missing/not signed so excluded: 1 1000 9 5028 9 416 5 219 9 611 (DOB also must be incorrect so left as sys missing) Missing DOB and Dates of consultation + postcode and relative for those entered by hand. 10496 120 11024 6263 7312 3126 9433 9446

	11640 9625 10467 9659 5248 91990 95004 92050 92052 61405 Checked incorrect dates of birth/dates of consultation and changed for 9632 9419 11663 258 6284 2 1141 10 456 119 286 6255 6299 8384 9623 11620 91975 101910 Date of birth for 9 5005 deleted so now sys missing as cannot be correct as stated as 30.9.2010 which is after date of consultation and date of CRF. Date of birth for 1 1067 deleted so now sys missing as cannot be correct as stated as 28.12.2008 which is after date of consultation and date of CRF. Checked DOB/date of consultation for those with age>5 yrs. Changed incorrect DOBs for 1 1090 8 392 Exclude 7 334 and 7 347 10 458 as age>5
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET 15 03	Daysurine checks – minus numbers checked date consultation and date urine result. Errors corrected for 3 103 2 53

2011	4 195 1 27 1 647 5 1854 18 1831 18 1821 19 2008 Missing lab results found/rang labs to get for: 9 633 10 1909 10 455 18 1830 18 1831 No urine result found and nil on UHW path link for 9 634 and 9 5000 so urine sample info removed.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET 04 04 2011	No changes made
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET 11 04 2011	CID 19 PID 2009 – entered as no growth and no organism but has got growth of organism so changed.
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET 15 04 2011	Additional info from lab about count for PID 2009,2016, 2018 so entered into database. 2009 Aerococcus 10^4 – 10^5 2016 E.coli >10^5 2018 Citrobacter >10^5
R:\PCAPH\PCAPH\SEWTU Studies\EURICA\Main study\Analysis\MAIN ANALYSIS\FULL DATASET SPSS ANALYSIS\FULL DATASET 19 04 2011	Data cleaning from file (Teleform queries) Nurse 6 1340 - 1409
Full dataset with follow up data 06 03 2012 to start. Changes made and saved as Full dataset with follow up data 01 07 2012	Tel f/up odd cases listed as PID 720, 721,747,769,790,791,849,964. These aren't PID numbers. Checked ACCESS database with names. These are all the ID numbers assigned in ACCESS. Checked them all and matched ID, name and DOB. 720 = CID 10, PID 1901 721 = CID 10, PID 1903 747 = CID 10, PID 1919

	769 = CID 10, PID 1685 790 = CID 10, PID 1911 791 = CID 10, PID 1916 849 = CID 09, PID 1977 964 = CID 09, PID 964 Manually changed. Data for these for tel f/up added to correct CID/PID numbers Added 2 new variables and completed manually – was telephone f/up completed and reason it wasn't if it wasn't. PID 323 – 6 month follow up data but no CRF or tel f/up ?wrong PID number. Paper copy checked Manual data entry 15 850 – 874 and 18 1800-1832 and 9 1981-2057 and 1 3000 & 3003 and 9 5003 – 5029 and 1 1698 **F**ollowing initial frequency checks outlying values spotted so checked and corrected errors for 6 256 no errors 6 1344 no errors 6 1359 no errors 6 260 no errors 4 180 FU2ADM & FU3OOH errors changed. 4 154 FU1CON 23 CORRECT 9 633 FU2ADM error changed 1 1078 FU2ADM error changed 1 1649 FU2ADM error changed 1 1004 no errors 1 27 no errors 1 38 FU6REF error changed 10 494 URINE RESULTS ENTERED. 10 2053 FU2ADM AND FU5UR errors changed 10 472 FU5UR error changed 10 461 FU4AB & FU7INV errors changed & RESULTS ENTERED. 1 1064 FU5UR error changed 1 1089 FU4AB AND FU5UR errors changed 9 613 FU4AB AND FU5UR errors changed 6 284 FU5UR error changed & urine results entered. 6 271 no errors. Urine results entered.
Full dataset with follow up data 01 07 2012 to start. Changes made and saved as Full dataset with follow up data 08 06 2012	4 154,160 171, 180 have urine results in f/up recorded but info not given. Need to chase surgery. Checking through all FU forms any with results attached checked. Any with '6' entered on database checked due to several errors found and any with large numbers checked. Also all checked for FU6REF & FU7INV if =1 as several errors found here.

	If boxes not ticked or number entered assumed =0. CID 1 PID 1 checked. Date of first urine sample was entered incorrectly. Changed. 1 1085 FU4AB error changed. 1 1073 FU4AB error changed. 1 1079 FU1CON & FU3OOH errors changed. 1 1062 FU6REF error changed 1 1045 not all urine culture info added so this added. 1 1043 FU1CON & FU5UR errors changed. 1 1680 FU1CON error changed 1 1675 FU3OOH error changed 1 1642 FU4AB error changed 1 1641 FU6REF & FU7INV errors changed. 1 1631 FU1CON error changed 1 1629 FU6REF & FU7INV errors changed. 1 1627 FU4AB error changed 1 1626 FU6REF & FU7INV errors changed. 1 1625 FU1CON error changed. 1 3003 incorrect date of urine result. Changed. 2 52 urine and renal uss results added. 2 53 FU6REF error changed. 2 55 FU6REF error changed. 2 76 FU6REF & FU7INV errors changed 2 78 FU6REF & FU7INV errors changed 2 89 Results added. 2 92 FU6REF error changed. 2 1134 FU6REF & FU7INV errors changed 2 1153 incomplete info for results entered. Also wrong date. Errors changed. 3 130 FUUSS error changed. 4 166 FU6REF error changed 4 171 FU6REF error changed 6 252 FU6REF, FU7INV, FUUSS and date of 3rd test wrong. errors changed. 6 254 FU6REF & FU7INV errors changed. Wrong date for 1st test. 6 268 FU6REF & FU7INV errors changed. 6 269 FU6REF & FU7INV errors changed. 6 270 incorrect date for test. 6 272 incomplete info for test. Corrected. 6 273 incomplete info for test. Corrected. 6 274 incomplete info for test. Corrected. 6 275 incomplete info for test. Corrected. 6 276 FU6REF error changed. incomplete info for test. Corrected. 6 277 incomplete info for test. Corrected. 6 278 incomplete info for test. Corrected. 6 279 incomplete info for test. Corrected. 6 280 incomplete info for test. Corrected.

	6 282 incomplete info for test. Corrected. 6 283 incomplete info for test. Corrected. 6 285 incomplete info for test. Corrected. 6 286 incomplete info for test. Corrected. 6 287 incomplete info for test. Corrected. 6 288 incomplete info for test. Corrected. 6 290 incomplete info for test. Corrected. 6 291 incomplete info for test. Corrected. 6 293 incomplete info for test. Corrected. 6 294 incomplete info for test. Corrected. 6 295 incomplete info for test. Corrected. 6 297 FU6REF & FU7INV errors changed. incomplete info for test. Corrected. 6 298 incomplete info for test. Corrected. 6 299 incomplete info for test. Corrected. 6 300 incomplete info for test. Corrected.
Full dataset with follow up data 08 06 2012to start. Changes made and saved as Full dataset with follow up data 11 06 2012	6 1331 incomplete info for test. Corrected. 6 1332 incomplete info for test. Corrected. 6 1333 incomplete info for test. Corrected. 6 1334 incomplete info for test. Corrected. 6 1335 incomplete info for test. Corrected. 6 1336 incomplete info for test. Corrected. 6 1337 FU3OOH ERROR. incomplete info for test. Corrected. 6 1338 incomplete info for test. Corrected. 6 1340 incomplete info for test. Corrected. 6 1341 FU6REF & FU7INV errors; incomplete info for test. Corrected. 6 1342 incomplete info for test. Corrected. 6 1343 incomplete info for test. Corrected. 6 1344 incomplete info for test. Corrected. 6 1345 incomplete info for test. Corrected. 6 1347 incomplete info for test. Corrected. 6 1348 FU6REF & FU7INV errors incomplete info for test. Corrected. 6 1349 incomplete info for test. Corrected. 6 1350 incomplete info for test. Corrected. 6 1351 incomplete info for test. Corrected. 6 1352 incomplete info for test. Corrected. 6 1353 incomplete info for test. Corrected. 6 1354 incomplete info for test. Corrected. 6 1356 incomplete info for test. Corrected. 6 1357 incomplete info for test. Corrected. 6 1358 incomplete info for test. Corrected. 6 1359 incomplete info for test. Corrected. 6 1360 incomplete info for test. Corrected. 6 1361 incomplete info for test. Corrected. 6 1362 incomplete info for test. Corrected. 6 1363 incomplete info for test. Corrected.

	6 1365 incomplete info for test. Corrected. 6 1366 incomplete info for test. Corrected. 6 1367 incomplete info for test. Corrected. 6 1368 incomplete info for test. Corrected. 6 1369 incomplete info for test. Corrected. 6 1372 incomplete info for test. Corrected. 6 1374 incomplete info for test. Corrected. 6 1376 incomplete info for test. Corrected. 6 1377 incomplete info for test. Corrected. 6 1379 incomplete info for test. Corrected. 6 1380 incomplete info for test. Corrected. 6 1381 incomplete info for test. Corrected. 6 1383 incomplete info for test. Corrected. 6 1404 FU6REF & FU7INV errors incomplete info for test. Corrected. 6 1406 FU6REF & FU7INV errors incomplete info for test. Corrected. 6 1409 incomplete info for test. Corrected. 7 302 incomplete info for test. Corrected. 7 314 incomplete info for test. Corrected 7 315 incomplete info for test. Corrected 7 317 incomplete info for test. Corrected 7 319 incomplete info for test. Corrected 7 322 incomplete info for test. Corrected FU5UR CORRECTED 7 324 incomplete info for test. Corrected 7 326 incomplete info for test. Corrected 7 333 incomplete info for test. Corrected 7 334 incomplete info for test. Corrected 7 343 DATE ERROR ON TEST RESULT. CORRECTED 7 347 incomplete info for test. Corrected 7 556 ERROR TEST RESULT . CORRECTED 7 557 incomplete info for test. Corrected 8 363 FU6REF & FU7INV errors incomplete info for test. Corrected 8 358 errors and incomplete info for test. Corrected
Full dataset with follow up data 11 06 2012 to start. Changes made and saved as Full dataset with follow up data 18 06 2012	8 377 FU6REF error corrected New variables added: EXCLUDEFUP and EXCFUPREAS excluded from 6 month follow up and reason excluded from 6 month follow up. Because of 8 383 note on form that patient left practice half way through f/up period (08/09) – d/w KH ?multiply up ?exclude 8 386 FU1CON and FU7INV errors corrected 8 392 error in test result. Corrected 8 393 error in test result. Corrected 8 394 incomplete info for test. Corrected 8 396 incomplete info for test. Corrected

	9 418 FU6REF & FU7INV errors 9 618 NO INFO AT ALL SCANNED/ENTERED. 9 619 NO INFO AT ALL SCANNED/ENTERED 9 620 NO INFO AT ALL SCANNED/ENTERED 9 622 FU6REF & FU7INV errors 9 623 FU6REF & FU7INV errors 9 624 FU6REF & FU7INV errors 9 640 FU6REF & FU7INV errors 9 641 FU1CON error 9 646 FU2ADM error 9 654 FU6REF & FU7INV errors and test result not entered. 9 1954 FU6REF & FU7INV errors 9 1959 NO INFO AT ALL SCANNED/ENTERED 9 1964 NO INFO AT ALL SCANNED/ENTERED 9 1969 NO INFO AT ALL SCANNED/ENTERED 9 1970 NO INFO AT ALL SCANNED/ENTERED 9 1976 NO INFO AT ALL SCANNED/ENTERED 9 1977 NO INFO AT ALL SCANNED/ENTERED 9 2054 NO INFO AT ALL SCANNED/ENTERED 10 454 FU6REF & FU7INV errors 10 458 FU6REF & FU7INV errors & incomplete test result. 10 461 FU6REF & FU7INV errors & incomplete test result. 10 463 FU6REF & FU7INV errors & incomplete test result. 10 464 FU6REF & FU7INV errors & incomplete test result. 10 468 incomplete test result 10 469 excluded. Moved from surgery 18/6/2009 10 471 excluded. Moved from surgery 30/07/2009 10 472 incomplete test result 10 474 FU1CON error 10 480 incomplete test result 10 481 incomplete test result 10 482 incomplete test result 10 485 incomplete test result 10 492 FU6REF & FU7INV errors 10 1901 incomplete test result. REGDOB, REGDT & FU6FUP also missing. 10 1902 incomplete test result. 10 1903 FU1CON & FU5UR errors and REGDOB, REGDT & FU6FUP also missing. AND incomplete test results. 10 1911 incomplete test results. 10 1914 incomplete test results. 10 1915 incomplete test results. 10 1919 incomplete test results. 10 1925 FUINV error

	10 1929 incomplete test results. 10 1938 incomplete test results. 10 2058 FU6REF & FU7INV errors 10 2064 incomplete test results 10 2065 FU5UR error. 10 2072 incomplete test results
Full dataset with follow up data 18 06 2012to start. Changes made and saved as Full dataset with follow up data 22 06 2012	1 1099 FU4AB error. 1 1113 FUDAT1 date entered. Only listed 04/2009 so 01.04.2009 entered (not close to recruitment date). 7 302 FUDAT1 date entered. 9 1977 FUDAT1 entered. 10 1918 FUOOH 7 326 FU5UR, FU6REF, and FU7INV errors 6 298 FU2ADM 1 1102 FU6REF & FU7INV errors 9 1970 FU1CON error 7 345 FU5UR error 7 556 FU2ADM 3 127 FU5UR error 18 1828 FU1CON 9 407 FU1CON
Full dataset with follow up data 22 06 2012 to start. Changes made and saved as Full dataset with follow up data 25 06 2012	Checking date of urine results listed in follow up period and checking they are not giving the index urine. If date urine result (original urine result) and date of test 1 (FUP) is the same or within 1 day assumed it is the index urine and recode number of urine samples in f/up period accordingly. - New variable TRUEFUPUR which is YES if there is a f/up urine result listed which is truly a separate urine sample sent in the 6 mth f/up period and not an index urine sample NB this still=1 if the f/up urine sample was a requested repeat. New variable on how many days after index consultation will be created. DURING CHECKING 1 39 Date discrepancy between original repeat sample date and f/up sample date but result the same. Checked. Error on f/up – should be 29/8/08 so changed. 4 160 error with urine result date. Changed.
Full dataset with follow up data 25 06 2012 to start. Changes made and saved as Full dataset with follow up	7 340 date f/up urine result checked. Incorrect. Corrected. 6 295 date f/up urine result checked. Incorrect.

data 02 07 2012	Corrected. 4 checked with Clifton practice as incomplete results given. 4 180 incomplete results. Changed. 4 154 incomplete results. Changed 4 160 result 29/12/2008 listed but not given. Added. 4 171 incomplete results. Changed 2 checked with PM at Highlight as incomplete results 9 654 urine results had no date. Checked and added. 9 1969 urine results indicated but no result given. Checked and added.

Appendix 4.16: Data cleaning decision rules

EURICA DATA-CLEANING DECISION RULES

KO = Kathy O'Brien
KH = Kerry Hood

Date agreed	Agreed by	Decision rule
28/05/2010	KO & KH	If 'Yes' and 'No' both ticked for an answer input as missing '-999'
28/05/2010	KO & KH	If 'No' and 'Not applicable' both ticked for an answer input as 'No'
28/05/2010	KO & KH	Q 51 and 71, where a numerical value for a temperature is required in °C, if the value is >90 and <110 this can be considered to be °F and converted into °C and entered into the database.
28/05/2010	KO & KH	Q 52 and 85 (severity scales) if 2 adjacent boxes are ticked, the ½ way value will be inserted (i.e. if '2' and '3' are ticked, then '2.5' will be entered into the database.
28/05/2010	KO & KH	Q52 and 85. If 2 non-adjacent boxes are ticked, this will be entered as missing/left blank.
28/05/2010	KO & KH	Any additional free text written outside of boxes will be entered into the database as a new variable called 'additional comments'
01/06/2010	KO & KH	If Q50 freetext then Q50 any other symptoms can be inserted as 'yes'
04/06/2010	KO & KH	Q63 approx how many weeks did pregnancy last. If gives range e.g. 36-38, mid-point will be inserted e.g. 37
04/06/2010	KO & KH	Q69 number of episodes of UTI if put 10+ or more than 10 or approx 10, then enter 10.
15/06/2010	KO & KH	Q53 and Q54 – if only put in day of date of when had medication can insert month and year according to date of illness onset if makes sense
15/06/2010	KO & KH	Q69 number of UTI episodes if they haven't entered a number but instead put '++' or 'many' then entered as -999 for missing data and added to freetext variable
8/7/2010	KO & KH	Q69 age of first UTI if number inserted with freetext outside e.g. 18 in box and months written outside, this is changed to a figure for number of years i.e. 1.5 yrs.

Appendix 4.17: STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 5: Appendices relating to Chapter 5: Results

Appendix 5.1: Calculation of confidence intervals for prevalence and ICC

Appendix 5.2: Histograms of continuous variables

Appendix 5.3: Calculations of probabilities of UTI based on the logistic regression model

Appendix 5.1: Calculation of confidence intervals for prevalence and ICC

Calculation of the prevalence in the population (population proportion) using the sample proportion and calculation of the ICC (Intraclass coefficient)

The standard error of the sample proportion needs to be calculated first:

If p = sample proportion = 35/597 = 0.0586

And Π = population proportion

The standard error of p can be calculated with the following equation:

SE (p) = $\sqrt{}$ Π(1- Π)/ $\sqrt{}$n

Best approximation of Π is p

$\sqrt{}$p = 0.2421

1-p = 0.9414

$\sqrt{}$n = 24.434

Table showing standard deviation of the population and sample.

	Population	**Sample**
Proportion	Π	p
Standard deviation	$\sqrt{}$ Π(1- Π)	$\sqrt{}$p(1-p) = 0.2279
	Standard error	$\sqrt{}$p(1-p)/$\sqrt{}$n = 0.0093

I can then calculate the 95% confidence intervals for the population proportion using the sample proportion:

95% CI= p +/- 1.96 x SE (p)

=p+/- 1.96 $\sqrt{}$ [p (1-p)/n]

= 0.0586+/- 0.0183

=0.0403 – 0.0769 i.e. the 95% CI for p using this method is 0.043-0.077

Calculation of the ICC and adjustment for cluster size

ICC adjusting for cluster sizes:

ICC (ρ) = MSC –MSW

MSC + (m_0-1) MSW

Where MSC =mean square between groups and MSW = mean square within groups)

And where

$$m_0 = \overline{m} - \sum_{j=1}^{k} \frac{(mj - \overline{m})^2}{(k-1)M}$$

Where k is number of clusters (13) and M is total number of individuals in sample (597) and mj is the number in each of the clusters. $\overline{m}$ is average cluster size = $\frac{M}{k}$ =597/13 = 45.923

This makes (k-1) (M) = 12x597=7164

The table below shows my interim calculations for the final equation

Practice (CID)	**Total number (mj)**	**(Mj-$\overline{m}$)^2**	**(Mj-$\overline{m}$)^2/ (k-1)(M)**
1	143	9423.944	1.315458
2	60	1981.162	0.027661
3	25	437.772	0.061107
4	35	119.312	0.016654
5	21	621.156	0.086705
6	80	1161.242	0.162094
7	29	286.388	0.039976
8	21	621.156	0.086705
9	87	1687.320	0.235528
10	56	101.546	0.014174
15	18	779.694	0.108835
18	12	1150.770	0.160632
19	10	1290.462	0.180131
Total	597		2.49566

M_0 = 45.923 – 2.49566 = 43.42734

So, to put this all in to the original equation to calculate ICC:

ICC (ρ) = MSC –MSW

MSC + (m_0-1) MSW

MSC (mean square between groups) = 68.660 (F=3.555 Sig 0.060)

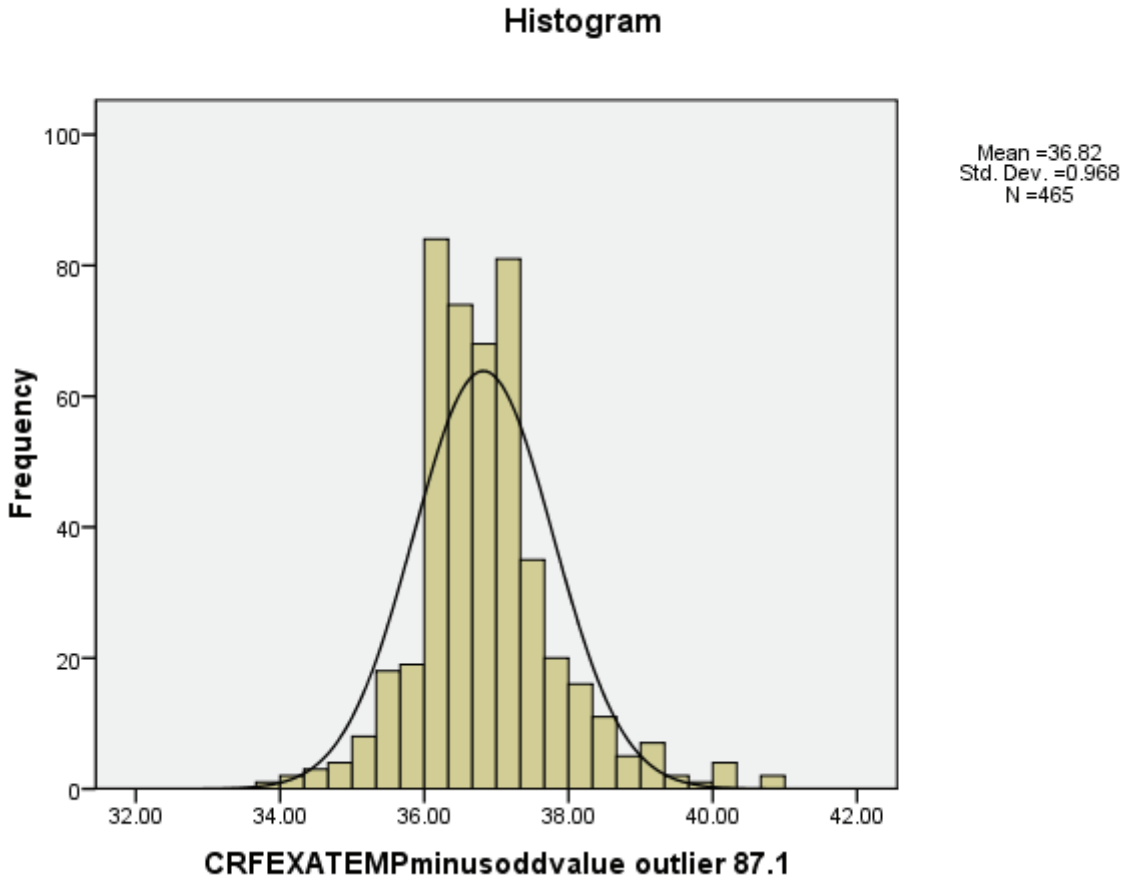
MSW (mean square within groups) = 19.315

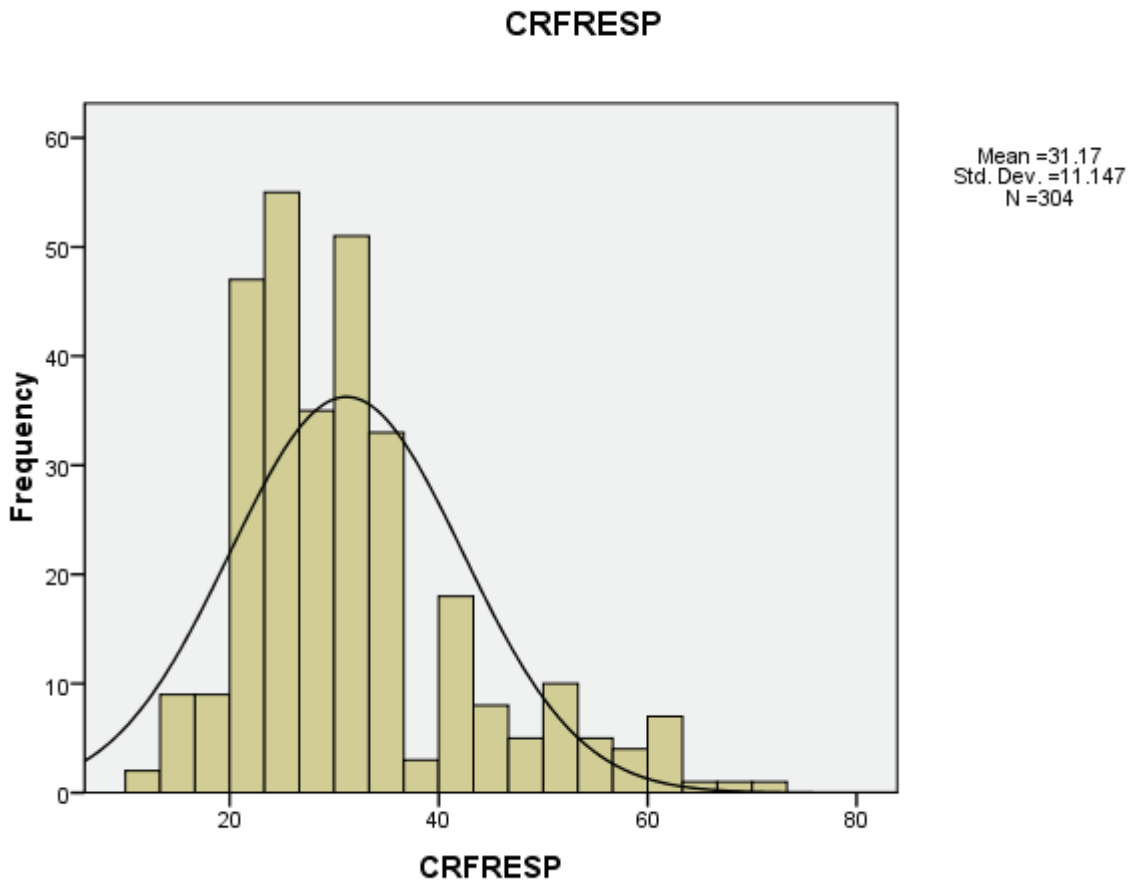
ρ = 68.660-19.315

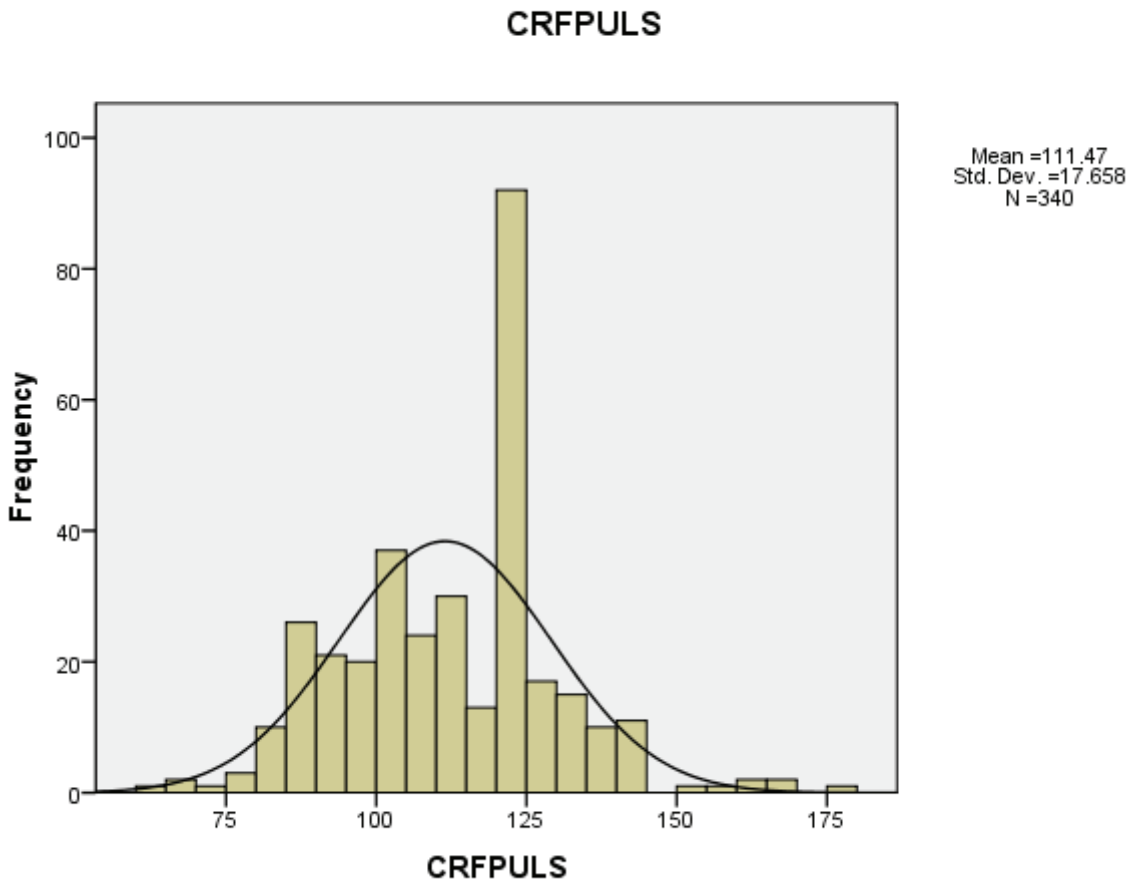
68.660 + (43.42734-1) x 19.315

Giving an ICC = 49.345/888.1440721 = 0.05556

Appendix 5.2: Histograms of continuous variables
Histograms




CRFRESP
Mean =31.17
Std. Dev. =11.147
N =304
Frequency
60
50
40
30
20
10
0
20
40
60
80
CRFRESP



Temperature was normally distributed. Respiratory rate had a skewed distribution. Pulse rate did not seem to be normally distributed at first. However, the distribution looks symmetrical and as if it would be a normal distribution if it was not for a large peak at 120-125 beats per minute and a much lower frequency of pulses at 115-120. This may be due to the way pulse rate is often measured in clinical practice where the beats are measured for 15 seconds and then multiplied by 4 to get the pulse rate for a minute. 120 divides perfectly by 4 to 30. Some may have rounded up or down to get a number which was easy to multiply by 4. Mean and medians were almost identical at 111.47 and 112.0 respectively. It was considered to be normally distributed for the statistical tests.

Appendix 5.3: Calculations of probabilities of UTI based on the logistic regression model

To calculate the confidence intervals for the probabilities of UTI predicted by the model, I needed to calculate the 95% confidence intervals for B (not given in the SPSS output).

95% confidence intervals for B calculated by B +/- 1.96 x S.E:

Urinary frequency:

0.966 +/- 1.96 x 0.398 = 0.966 +/- 0.78008 = 0.18592 - 1.74608

Pain:

1.194 +/- 1.96 x 0.554 = 1.194 +/- 1.08584 = 0.10816 - 2.27984

Age <3/12

1.712 +/- 1.96 x 0.680 = 1.712 +/- 1.33280 = 0.37920 - 3.04480

Age 3/12 – 3 yrs

0.865 +/- 1.96 x 0.451 = 0.865 +/- 0.88396 = -0.01896 - 1.74896

Constant

-3.781 +/- 1.96 x 0.427 = -3.781 +/- 0.83692 = -4.61792 - -2.94408

Model:

Symptom/characteristic	B	S.E.	95% CI for B		Odds ratio	p-value	95% CI for odds ratio
			Lower	Upper			
Urinary frequency	0.966	0.398	0.186	1.746	2.63	0.015	1.20-5.74
Pain on passing urine	1.194	0.554	0.181	2.280	3.30	0.031	1.12-9.76
NICE age range<3/12	1.712	0.680	0.379	3.045	5.54	0.012	1.46-21.0
NICE age range 3/12-3 years	0.865	0.451	0.0190	1.749	2.38	0.055	0.98-5.75
Constant	-3.781	0.427	-4.618	-2.944			

P=0.002

To calculate the probability of UTI using the model:

$$p\,(UTI) = 1/1 + e^{-(-3.781 + 0.966[freq]+1.194[pain]+1.712[age <3 mths]+0.865[age 3mths-3yrs])}$$

Age less than 3 months old

$$p\,(UTI) = 1/1 + e^{-(-3.781 + 0.966[freq]+1.194[pain]+1.712)}$$

No symptoms: $p\,(UTI) = 1/1 + e^{-(-3.871+1.712)} = 10.35\%$

Freq and pain: $p\,(UTI) = 1/1 + e^{-(-3.781 + 0.966[freq]+1.194[pain]+1.712)} = 31.47\%$

Frequency only: $p\,(UTI) = 1/1 + e^{-(-3.781 + 0.966[freq]+1.194[pain]+1.712)} = 25.27\%$

Pain only: p (UTI) =1/1 + $e^{-(-3.781 +1.194[pain]+1.712)}$= 29.42%

Age between 3 months and 3 years old

p(UTI) = 1/1 + $e^{-(-3.781 + 0.966[freq]+1.194[pain]+0.865)}$

No symptoms: p (UTI) =1/1 + $e^{-(-3.781 + 0.865)}$ = 5.14%

Freq and pain: p (UTI) =1/1 + $e^{-(-3.781 + 0.966[freq]+1.194[pain]+0.865)}$ =31.95 %

Freq only: p (UTI) =1/1 + $e^{-(-3.781 + 0.966+ 0.865)}$ = 12.46%

Pain only: p (UTI) =1/1 + $e^{-(-3.781 + 1.194+0.865)}$ = 15.16%

Age greater than or equal to 3 years old

p (UTI) = 1/1 + $e^{-(-3.781 + 0.966[freq]+1.194[pain])}$

No symptoms: p (UTI) =1/1 + $e^{-(-3.781)}$ =2.23 %

Freq & pain: p (UTI) =1/1 + $e^{-(-3.781 + 0.966+1.194)}$= 16.51%

Freq only: p (UTI) =1/1 + $e^{-(-3.781 + 0.966)}$ = 5.65%

Pain only: p (UTI) =1/1 + $e^{-(-3.781 + 1.194)}$ =6.70 %

95% confidence intervals: lower:

Symptom/characteristic	B	S.E.	95% CI for B	
			Lower	Upper
Urinary frequency	0.966	0.398	0.186	1.746
Pain on passing urine	1.194	0.554	0.181	2.280
NICE age range<3/12	1.712	0.680	0.379	3.045
NICE age range 3/12-3 years	0.865	0.451	0.0190	1.749
Constant	-3.781	0.427	-4.618	-2.944

p(UTI) = 1/1 + $e^{-(-4.618 + 0.186[freq]+1.181[pain]+0.379[age <3 mths]+0.0190[age 3mths-3yrs])}$

Age less than 3 months old

p (UTI) = 1/1 + $e^{-(-4.618 + 0.186[freq]+1.181[pain]+0.379)}$

No symptoms: p (UTI) =1/1 + $e^{-(-4.618 +0.379)}$ = 1.4%

Freq and pain: p (UTI) =1/1 + $e^{-(-4.618 + 0.186+1.181+0.379)}$ =5.4 %

Frequency only: p (UTI) =1/1 + $e^{-(-4.618 + 0.186+0.379)}$ = 1.7%

Pain only: p (UTI) =1/1 + $e^{-(-4.618 + 1.181+0.379)}$ = 4.5%

Age between 3 months and 3 years old

p (UTI) = 1/1 + $e^{-(-4.618 + 0.186[freq]+1.181[pain]+ 0.0190)}$

No symptoms: p (UTI) =1/1 + $e^{-(-4.618 + 0.0190)}$ = 1.0%

Freq and pain: p (UTI) =1/1 + $e^{-(-4.618 + 0.186+1.181+ 0.0190)}$= 3.8%

Freq only: p (UTI) =1/1 + $e^{-(-4.618 + 0.186+ 0.0190)}$ = 1.2%

Pain only: p (UTI) =1/1 + $e^{-(-4.618 + 1.181+0.0190)}$ = 3.2%

Age greater than or equal to 3 years old

p (UTI) = 1/1 + $e^{-(-4.618 + 0.186[freq]+1.181[pain]+0.379)}$

No symptoms: p (UTI) =1/1 + $e^{-(-4.618)}$ =1.0 %

Freq & pain: p (UTI) =1/1 + $e^{-(-4.618 + 0.186+1.181+0.379)}$ =5.4 %

Freq only: p (UTI) =1/1 + $e^{-(-4.618 + 0.186+0.379)}$ =1.7 %

Pain only: p (UTI) =1/1 + $e^{-(-4.618 + 1.181+0.379)}$ = 4.5%

Symptom/characteristic	B	S.E.	95% CI for B	
			Lower	Upper
Urinary frequency	0.966	0.398	0.186	1.746
Pain on passing urine	1.194	0.554	0.181	2.280
NICE age range<3/12	1.712	0.680	0.379	3.045
NICE age range 3/12-3 years	0.865	0.451	0.0190	1.749
Constant	-3.781	0.427	-4.618	-2.944

95% CI upper:

p(UTI) = 1/1 + $e^{-(-2.944+ 1.746[freq]+2.280[pain]+3.045[age <3 mths]+1.749[age 3mths-3yrs])}$

Age less than 3 months old

p (UTI) = 1/1 + $e^{-(-2.944+ 1.746[freq]+2.280[pain]+3.045)}$

No symptoms: p (UTI) =1/1 + $e^{-(-2.944+ +3.045)}$ = 52.5%

Freq and pain: p (UTI) =1/1 + $e^{-(-2.944+ 1.746+2.280+3.045)}$ =98.4%

Frequency only: p (UTI) =1/1 + $e^{-(-2.944+ 1.746+3.045)}$ = 86.4%

Pain only: p (UTI) =1/1 + $e^{-(-2.944+ 2.280+3.045)}$ = 91.5%

Age between 3 months and 3 years old

$$p(UTI) = 1/1 + e^{-(-2.944 + 1.746[freq] + 2.280[pain] + 1.749)}$$

No symptoms: $p(UTI) = 1/1 + e^{-(-2.944 + 1.749)} = 23.2\%$

Freq and pain: $p(UTI) = 1/1 + e^{-(-2.944 + 1.746 + 2.280 + 1.749)} = 94.4\%$

Freq only: $p(UTI) = 1/1 + e^{-(-2.944 + 1.746 + 1.749)} = 63.4\%$

Pain only: $p(UTI) = 1/1 + e^{-(-2.944 + 2.280 + 1.749)} = 74.7\%$

Age greater than or equal to 3 years old

$$p(UTI) = 1/1 + e^{-(-2.944 + 1.746[freq] + 2.280[pain])}$$

No symptoms: $p(UTI) = 1/1 + e^{-(-2.944)} = 5.0\ \%$

Freq & pain: $p(UTI) = 1/1 + e^{-(-2.944 + 1.746 + 2.280)} = 74.7\ \%$

Freq only: $p(UTI) = 1/1 + e^{-(-2.944 + 1.746)} = 23.2\%$

Pain only: $p(UTI) = 1/1 + e^{-(-2.944 + 2.280)} = 34.0\%$