Urinary tract infections in young children: optimising diagnosis with effective and cost-effective urine sample collection

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ABSTRACT

BACKGROUND

Urinary tract infections (UTIs) are very common in young children, but hard to diagnose, and easily missed. Diagnosis is important: if untreated UTI can cause sepsis and permanent kidney scarring. Many young children with unexplained fever must have a urine sample tested to check for potential UTI.

The problem is that collecting urine samples from young pre-continent children is extremely difficult. Existing collection methods all have limitations. Standard care in Australia of waiting for a clean catch is time-consuming and often unsuccessful. Urine bags have unacceptably high contamination. Catheter and needle procedures are painful and distressing, and require expertise and equipment to perform. Suboptimal practice compromises patient care and wastes healthcare resources.

AIMS & METHODS

The doctoral research had the overall objective to improve non-invasive urine sample collection for young pre-continent children.

Specific aims were to discover:

1. A quick, simple and effective non-invasive collection method
2. Cost-effectiveness of current and new collection methods
3. Which collection methods are practical in the primary care setting
4. Knowledge translation of findings into practice

These aims were examined with the following research methodologies:

1. Two clinical trials of a novel voiding stimulation method
2. Economic evaluation of existing and new collection methods
3. Qualitative study in Australian general practice
4. Local guideline update and development of consumer resources

RESULTS

The novel Quick-Wee voiding stimulation method was conceptualised, using cold wet gauze to gently rub the suprapubic region. This triggers cutaneous bladder reflexes for faster and more successful urine sample collection. A pilot study (n=40) demonstrated the method was feasible. A randomised trial (n=354) demonstrated significantly higher success in collecting a urine sample within 5 minutes, and significantly higher parental and clinician satisfaction, compared to standard clean catch practice.

An economic evaluation comprehensively modelled the costs and cost-effectiveness to collect a definitive sample for all common urine sample collection methods. Overall, catheterisation was the favoured collection method, Quick-Wee the favoured non-invasive method, and urine bags were the most expensive method. This is the first cost-effectiveness analysis of its kind, filling a significant evidence gap, and identifying potential cost savings.

A qualitative study explored the barriers and enablers to collecting urine samples from young children in Australian general practice. Non-invasive methods were strongly favoured and invasive methods were rarely used. Key barriers included time and space constraints in clinics. Key enablers included parental motivation, education handouts and voiding stimulation methods. These important insights can inform policy, education and future research.

Knowledge translation activities were undertaken including updating statewide guidelines and creating consumer resources. The Quick-Wee method is now recommended in guidelines across a range of settings internationally.

CONCLUSION

This body of work developed the new Quick-Wee voiding stimulation method and has shown it is more effective, more cost-effective, and more acceptable than standard care. It is gentle for children and simple for clinicians. This research has addressed key evidence gaps, contributing new knowledge to

optimise investigation of UTI in young children. Findings have changed practice and been implemented in policies and guidelines internationally.

DECLARATION

This is to certify that:

(i) the thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the preface;

(ii) due acknowledgement has been made in the text to all other material used;

(iii) the thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies and appendices.

Jonathan Kaufman

15th May 2020

PREFACE

PUBLICATIONS ARISING FROM THE DOCTORAL RESEARCH

This doctoral thesis includes 9 original first author research or review publications in peer-reviewed journals, that arose directly from the doctoral candidature.

For each publication the doctoral candidate designed the study or review, conducted the required searches and critical appraisal of the literature, wrote all required protocols, sought all ethics approvals required, led data collection, and analysed and interpreted results. The doctoral candidate wrote the first draft of each manuscript, contributed more than 50% of the content of each manuscript, performed subsequent editing in response to co-author feedback, submitted all articles for publication in peer reviewed journals, and completed all responses to peer review.

Multiple co-authors contributed to the published manuscripts, including guidance on study design, guidance on planning data collection and analysis, feedback on protocols, assistance with clinical data collection and statistical analysis, feedback on manuscript drafts, and further feedback following peer review. A detailed description of specific co-author contributions to each publication is outlined where the publication appears in the thesis, or in the study roles and responsibilities section of that chapter. All co-authors provided consent for their inclusion in this thesis and completed the required University of Melbourne Co-Author Authorisation Form.

1. **Kaufman J**, Temple-Smith M, Sanci L. Urinary tract infections in children: an overview of diagnosis and management. *BMJ Paediatrics Open* 2019;3:487. doi: 10.1136/bmjpo-2019-000487

2. **Kaufman J**, Tosif S, Fitzpatrick P, Hopper S, Donath S, Bryant P, Babl F. QuickWee: a novel non-invasive urine collection method. *Emergency Medicine Journal* 2017 Jan;34(1):63-64. doi: 10.1136/emermed-2016-206000

3. **Kaufman J**, Fitzpatrick F, Tosif T, Hopper S, Bryant P, Donath S, Babl F. The QuickWee trial: protocol for a randomised controlled trial of gentle suprapubic cutaneous stimulation to hasten non-invasive urine collection from infants. *BMJ Open* 2016;6:e011357. doi: 10.1136/bmjopen-2016-011357

4. **Kaufman J**, Tosif S, Fitzpatrick P, Hopper S, Donath S, Bryant P, Babl F. Faster clean catch urine collection from infants: the Quick-Wee randomised controlled trial. *The BMJ*, 2017;357:j1341. doi: 10.1136/bmj.j1341

5. **Kaufman J**, Knight A, Bryant P, Babl F, Dalziel K. Liquid gold: the cost-effectiveness of urine sample collection methods for young precontinent children. *Archives of Disease of Childhood*, 2020;105:253-259: doi: 10.1136/archdischild-2019-317561

6. **Kaufman J**, Temple-Smith M, Sanci L. What's the catch? Urine sample collection from young pre-continent children: a qualitative study in primary care. *British Journal of General Practice Open*. In press (accepted for publication 28th February 2020). doi: 10.3399/bjgpopen20X101060

7. **Kaufman J.** How to… collect urine samples from young children. *Archives of Disease in Childhood Education & Practice*, Published Online First: 23 August 2019. doi: 10.1136/archdischild-2019-317237

8. **Kaufman J**, Temple-Smith M, Sanci L. Urine sample collection from young pre-continent children. Common methods and the new Quick-Wee technique. *British Journal of General Practice* 2020; 70 (690): 42-43. doi: 10.3399/bjgp20X707705

9. **Kaufman J**, Tosif S, Duke T. Voiding stimulation methods for collecting urine from young pre-continent children [Letter to the editor] *Paediatrics and International Child Health*, 2017; 37(4), pp. 298–299. doi: 10.1080/20469047.2017.1399650

CO-AUTHORED PUBLICATIONS ASSOCIATED WITH THE DOCTORAL RESEARCH

Two associated co-authored publications are included in the appendices of this thesis.

I. Tosif S, **Kaufman J**, Fitzpatrick P, Hopper S, Hoq M, Donath S, Babl F. Clean Catch Urine Collection: Time taken and diagnostic implication. A Prospective Observational Study. *Journal of Paediatrics & Child Health* 2017 Oct;53(10):970-975. doi: 10.1111/jpc.13595

II. Waterham M, **Kaufman J**, Gibb S. Childhood constipation. *Australian Family Physician*. Vol. 46, No. 12, Dec 2017: 908-912. Available from: www.racgp.org.au/afp/2017/december/childhood-constipation/

CONFERENCE PRESENTATIONS ARISING FROM THE DOCTORAL RESEARCH

12 research presentations were delivered at national and international conferences:

INTERNATIONAL

1. **Kaufman J**, Fitzpatrick P, Tosif S, Hopper S, Bryant P, Babl F. Faster non-invasive urine collection from infants: the Quick-Wee randomised controlled trial. Oral Presentation. Pediatric Academic Societies Annual Meeting, San Francisco, USA 2017

2. **Kaufman J**, Fitzpatrick P, Tosif S, Hopper S, Bryant P, Babl F. Faster clean catch urine collection from infants: the Quick-Wee randomised controlled trial. Oral Presentation. Royal College of Paediatrics & Child Health Conference, Birmingham, UK 2017

3. **Kaufman J**, Fitzpatrick P, Tosif S, Hopper S, Bryant P, Babl F. The Quick-Wee RCT: A Novel Stimulation Method For Clean Catch Urine Collection in

Infants. Oral Presentation. Congress of the European Academy of Paediatric Societies, Geneva, Switzerland 2016 (presented by Dr S Hopper)

4. **Kaufman J**, Fitzpatrick P, Tosif S, Hopper S, Bryant P, Babl F. Quick-Wee: A Novel Non-Invasive Urine Collection Method For Infants in the Paediatric Emergency Department. Poster Presentation. Canadian Pediatric Society Annual Conference, Charlottetown, Canada 2016

NATIONAL

5. **Kaufman J**, Temple-Smith M, Sanci L. What's The Catch: Barriers and enablers to collecting urine samples from young pre-continent children in primary care. Oral Presentation. Health Services Research Association of Australia and New Zealand Conference, Auckland, New Zealand 2019

6**. Kaufman J**, Temple-Smith M, Sanci L. Yes Wee Can: saving time and money with improved urine sample collection for young pre-continent children. Oral Presentation (3MT). Health Services Research Association of Australia and New Zealand Conference, Auckland, New Zealand 2019

7. **Kaufman J**, Temple-Smith M, Sanci L. What's The Catch: Barriers and enablers to collecting urine samples from young pre-continent children in primary care. Poster Presentation. Australasian Association for Academic Primary Care, Adelaide 2019

8. **Kaufman J**, Temple-Smith M, Sanci L. Yes Wee Can: better urine sample collection for young pre-continent children. Oral Presentation. Choosing Wisely Australia National Meeting, Melbourne 2019

9. **Kaufman J**, Knight J, Bryant P, Babl F, Dalziel K. Liquid Gold: the cost effectiveness of urine sample collection methods for young pre-continent children. Poster Presentation. Royal Australasian College of Physicians Congress, Sydney 2018

10. **Kaufman J**, Fitzpatrick P, Tosif S, Hopper S, Bryant P, Babl F. The Quick-Wee RCT: A Novel Stimulation Method For Quick Clean Catch Urine

Collection in Infants. Oral Presentation. Australasian College For Emergency Medicine Annual Scientific Meeting, Queenstown, New Zealand 2016

11. **Kaufman J**, Fitzpatrick P, Tosif S, Hopper S, Bryant P, Babl F. Quick-Wee: Catching Urine Samples Quickly From Infants in the Paediatric Emergency Department. Oral Presentation. Royal Australasian College of Physicians Congress, Adelaide 2016

12. **Kaufman J**, Tosif S, Fitzpatrick P, Hopper S, Bryant P, Babl F. Quick-Wee: Catching Urine Samples Quickly in Young Children in the Emergency Department. Oral Presentation. Australasian College for Emergency Medicine Annual Scientific Meeting, Brisbane 2015

LOCAL

Research abstracts were presented at a further 7 local research conferences and symposia.

DOCTORAL RESEARCH FUNDING

The doctoral candidate received the following philanthropic research grant to support the Quick-Wee randomised controlled trial:

1. **Research Grant**: $26,266 Shepherd Foundation (2015)

DOCTORAL RESEARCH SCHOLARSHIPS & TRAVEL GRANTS

The doctoral candidate received the following 10 scholarships and travel grants to provide a PhD stipend and to support research related travel and course attendance.

1. **Postgraduate Health Research Scholarship**: Murdoch Children's Research Institute (2017-20)

2. **Australian Government Research Training Program Scholarship**: University of Melbourne (2017-20)

3. **Graduate Research Travel Grant**: Department of General Practice, University of Melbourne (2019)

4. **Course Scholarship**: Advanced Clinical Trial Design, University of Melbourne (2019)

5. **Student Conference Support Award**: Murdoch Children's Research Institute (2017)

6. **Henry and Rachel Ackman Travelling Scholarship**: University of Melbourne (2017)

7. **Basser Research Entry Scholarship**: Royal Australasian College of Physicians (2016)

8. **Jeannie Poolman Travelling Scholarship**: Royal Children's Hospital, Melbourne (2016)

9. **Doctor in Training Research Scholarship**: Avant Mutual Group (2015)

10. **Medical Staff Association Travel Scholarship**: Royal Children's Hospital, Melbourne (2015)

DOCTORAL RESEARCH PRIZES & AWARDS

The doctoral candidate received the following 22 prizes and awards for the doctoral research.

INTERNATIONAL

1. **Joan Robson Paediatric Emergency Medicine Research Prize**: Royal College of Paediatrics & Child Health UK (2017)

2. **Prize in Paediatric Emergency Medicine**: PREDICT Paediatric Research Network (2016)

NATIONAL

3. **Sustainable Healthcare Award**: Bond University (2019)

4. **Best Paper (PhD) Award**: Health Services Research Association of Australia & New Zealand (2019)

5. **Audience Choice Award (3 Minute Thesis)**: Health Services Research Association of Australia & New Zealand (2019)

6. **Best Student Abstract**: Choosing Wisely Australia National Meeting (2019)

7. **Best Poster Prize (Paediatrics)**: Royal Australasian College of Physicians National Congress (2018)

8. **Best Trainee Paper Prize**: Australasian College of Emergency Medicine Annual Scientific Meeting (2016)

9. **Paediatric Trainee Research Award for Excellence**: Royal Australasian College of Physicians (2015)

10. **Best Trainee Paper Prize**: Australasian College of Emergency Medicine Annual Scientific Meeting (2015)

STATE

11. **Finalist: Premier's Award for Health and Medical Research**: Victoria (2020)

12. **Finalist: Improving Healthcare Through Clinical Research**: Victorian Public Healthcare Awards (2017)

13. **Best 1st Year Student Presentation Award**: Australian Society for Medical Research Symposium (2016)

LOCAL

14. **Best Short Talk**: Faculty of Medicine Early Career Research Symposium, University of Melbourne (2019)

15. **Best Student Publication Prize**: Murdoch Children's Research Institute (2018)

16. **Best Poster Prize**: Faculty of Medicine Early Career Research Symposium, University of Melbourne (2018)

17. **Audience Choice Poster Prize**: Faculty of Medicine Early Career Research Symposium, University of Melbourne (2018)

18. **Melbourne Medical School Student Publication Prize**: University of Melbourne (2018)

19. **Equal Winner: 3 Minute Thesis**: Round 4, School of Paediatrics, University of Melbourne (2018)

20. **People's Choice Award: 3 Minute Thesis**: Round 4, School of Paediatrics, University of Melbourne (2018)

21. **2nd Prize (1st Year PhD category)**: Murdoch Children's Research Institute Student Symposium (2016)

22. **Advanced Trainee Research Prize**: Royal Children's Hospital, Melbourne (2015)

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This PhD has been a long journey: from the original idea for a voiding stimulation method which popped into my head during night shift as a junior doctor, to deciding to turn that idea into a research doctorate, to planning and carrying out the research, to submitting this thesis. Many people have helped along the way and I couldn't have done it without them.

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Thank you to all the organisations that provided practical and in-kind support for the research: the University of Melbourne Departments of General Practice and Paediatrics, the Royal Children's Hospital Emergency Department, Murdoch Children's Research Institute, the Shepherd Foundation, Avant, and the Royal Australasian College of Physicians.

And a huge and heartfelt thank you to all the nurses, doctors, children and families who were a part of the research. None of these studies would have been possible without your generous participation.

The PhD road has been a bumpy one. Many times it's been tough to keep going, right up to finishing the thesis amidst the busyness and disruption of preparation and clinical work during the COVID-19 pandemic.

I have learned a lot from this research apprenticeship. Thank you to everyone who has supported, encouraged, advised and guided me to learn in particular these three valuable lessons for research:

1. Be curious: If you see something that is missing, doesn't make sense or could be improved, ask why, and respectfully challenge dogma and hubris.

2. Be kind: Always be generous and support your colleagues. What's the point of being successful if you have to trample over others to get there.

3. Be persistent: People might say it won't work or it can't be done. They may or may not be right. The reward comes from the sincere effort, not the result.

DEDICATION

This thesis is dedicated to all the healthcare workers, scientists and so many others around the world who have taken up the fight against the COVID-19 pandemic.

And to those who will not fight again.

In necessariis unitas, in omnibus caritas.

In necessary things unity, in all things charity.

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THIRD PARTY COPYRIGHT MATERIAL INCLUDED IN THE THESIS

Citation information for third party copyright material	Location of item in thesis	Permission granted Y/N
Labrosse et al. Evaluation of a New Strategy for Clean-Catch Urine in Infants. Pediatrics. 2016; 138(3):e20160573. Figure 1.	Section 4.7.2, p98, Figure 8	Y
Dasgupta et al. The 'Queen Square bladder stimulator': a device for assisting emptying of the neurogenic bladder. Br J Urol. 1997Aug;80(2): 234-7. Figure 1.	Section 4.7.4, p106, Figure 9	Y

KEYWORDS

Urinary tract infection, diagnosis, infant, children, urine specimen collection

LIST OF ABBREVIATIONS

$AUD	Australian dollars
£GBP	British pounds
AAP	American Academy of Pediatrics
ANZCTR	Australia New Zealand Clinical Trials Registry
BBD	Bladder bowel dysfunction
BEACH	Bettering the Evaluation And Care of Health program
CCU	Clean catch urine
CFU	Colony forming unit
CHEERS	Consolidated Health Economic Evaluation Reporting Standard
CI	Confidence interval
CMV	Cytomegalovirus
CONSORT	Consolidated Standards Of Reporting Trials
CPG	Clinical practice guideline
CRF	Case record form
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
E.COLI	Escherichia coli
ED	Emergency department
ESBL	Extended spectrum beta lactamase
GFR	Glomerular filtration rate
GP	General practitioner
HTA	Health technology assessment
IQR	Interquartile range
KHI	Kids health information
KT	Knowledge translation
MCRI	Murdoch Children’s Research Institute

ML	Millilitre
MSU	Midstream urine
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
OECD	Organisation for Economic Co-operation and Development
PCR	Polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic reviews & Meta Analyses
PUO	Pyrexia of unknown origin
RCH	Royal Children's Hospital
RCT	Randomised controlled trial
REDCAP	Research Electronic Data Capture
SCI	Spinal cord injury
SPA	Suprapubic needle aspiration
SPIRIT	Standard Protocol Item Recommendations for Interventional Trials
UK	United Kingdom
US	United States of America
UTI	Urinary tract infection
VUR	Vesicoureteral reflux
WHO	World Health Organisation

Chapter 1 INTRODUCTION

1.1 PAEDIATRIC UTI AND DIAGNOSIS: A COMMON PROBLEM

Urinary tract infections (UTIs) are one of the most common bacterial infections of early childhood. Amongst the many febrile pre-continent infants and children who present for medical care, approximately 7% will have a UTI in developed countries, [1] with even higher prevalence in developing countries. [2] Timely diagnosis is important to avoid complications such as sepsis and permanent renal scarring. However the signs and symptoms of childhood UTI are frequently non-specific, and clinical diagnosis is unreliable. Therefore many young children with unexplained fever must have a urine sample collected to either make or exclude the UTI diagnosis. However despite UTI being one of the commonest infections of early childhood, we so often stumble at this crucial first step in evaluation.

The problem is that collecting the necessary urine samples from young pre-continent children is challenging. Current collection methods all have limitations. Non-invasive collection methods involve waiting for the child to void spontaneously, and then collecting urine with either an adhesive urine bag or an opportunistic ‘clean catch’ of the urine stream. These methods seem convenient, but are often time-consuming, unsuccessful, or corrupted by incidental skin flora contamination. [3] Invasive collection methods involve using urethral catheterisation or suprapubic needle aspiration to sample urine directly from the bladder. These methods can be more reliable, but require specific equipment and expertise that are not available in all settings, and cause pain and distress to the child. [4] The choice of collection method must therefore balance time, invasiveness, reliability and resources. Despite being such a common part of practice in paediatrics, emergency medicine and general practice, there is significant variation in international guideline recommendations, and parent and clinician preferences, for the optimal collection method.

Suboptimal sample collection is detrimental to patient care. Prolonged sample collection attempts are frustrating and waste time for parents and carers. Missed sample collection increases the likelihood of both missed diagnosis and misdiagnosis of UTI, delays timely and targeted treatment, and in turn increases inappropriate and untargeted antibiotic prescribing. Suboptimal sample collection is also detrimental to health service efficiency. Delays in sample collection prolongs hospital bed occupancy and increases patient stay in primary care clinics. Contaminated samples may necessitate subsequent presentations for re-evaluation and repeat sample collection. False positive results can trigger a cascade of unnecessary follow-up and further investigations. All of these issues unnecessarily increase the burden on patients, families and healthcare resources.

Sample collection from young pre-continent children may also be costly for the healthcare system. Many children with suspected UTI or unexplained fever need to have a urine sample collected. Urine sample collection methods all have different resource requirements and probabilities of successfully obtaining a definitive sample, but the costs and cost-effectiveness of collection methods are not known. Current guideline recommendations are not based on evidence of cost-effectiveness. Understanding these costs could inform recommendations, and lead to cost savings. For such a common procedure, even modest cost savings could be significant in the aggregate.

Finally, many of the febrile young children who require evaluation for UTI present for medical attention from primary care clinicians, and in the Australian healthcare system general practitioners play a central role in the delivery of primary healthcare to children. For the majority of children with lower urgency conditions such as unexplained fever, parents will seek care with their general practitioner in the first instance. [5] However general practice has unique time and resource constraints that influence which urine sample collection methods are possible and practical in this setting. This may not be considered in guidelines written from a hospital or specialist perspective. Data regarding the practicalities of investigating early childhood UTI in general

practice is limited, but could inform guidelines and identify opportunities for targeted future research.

Improved sample collection would have many benefits for children, parents and clinicians, though clinical practice has not advanced for many decades. Further research to improve collection is recognised in the literature as a research priority. The ideal solution would be a quick, simple and gentle way to collect the necessary samples.

1.2 OVERALL OBJECTIVE AND SCOPE OF THESIS

The overall objective of this doctoral research was to improve non-invasive urine sample collection for young pre-continent children.

The scope of the research was limited to pre-continent children being evaluated for potential UTI, which typically includes infants and young children less than 1-2 years of age. Evaluation of the effectiveness of collection methods considered clinical effectiveness, cost-effectiveness, and acceptability to clinicians and parents.

1.3 SPECIFIC RESEARCH AIMS

To address the overall objective, there were four specific research aims:

Aim 1: To develop a novel voiding stimulation method for faster and more effective non-invasive urine collection from young pre-continent children.

Aim 2: To understand the costs and cost-effectiveness of current urine sample collection methods used for young pre-continent children, as well as the newly developed method.

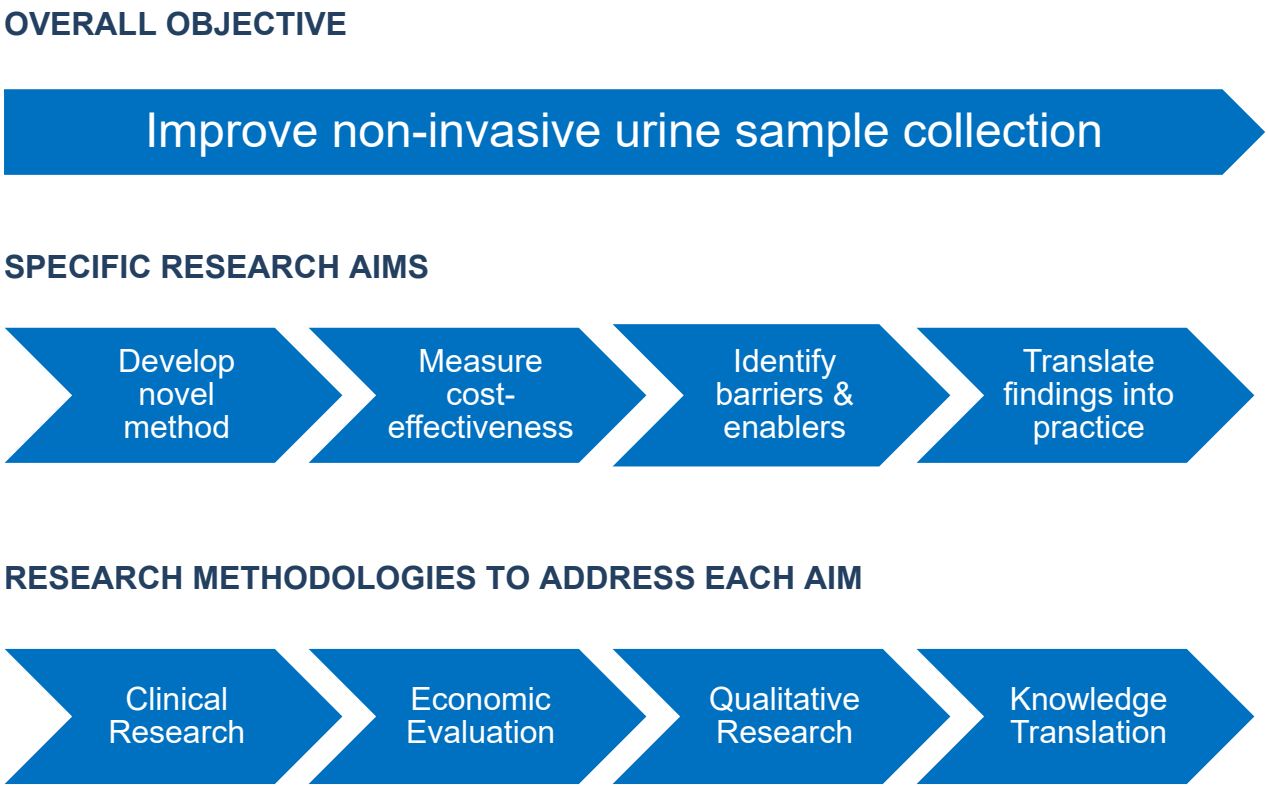
Aim 3: To explore the barriers and enablers to collecting urine samples from young pre-continent children from the perspective of primary care clinicians,

to understand which collection methods are practical in the primary care setting.

Aim 4: To facilitate translation of research findings into practice, policy and guidelines.

Each research aim had its own specific methodology and corresponding studies (Figure 1), which are described subsequently.

Figure 1: Thesis objective, aims and methodologies



1.4 THESIS STRUCTURE AND OVERVIEW

Chapter 2 provides a **background** and context for the body of research included in the doctoral thesis. This includes an overview of paediatric UTI, tests and diagnosis, and current urine sample collection methods. This provides a rationale for improving collection methods used for young pre-continent children, and justification for the research conducted during the PhD

candidature. The chapter includes content from a clinical review article published in *BMJ Paediatrics Open* (Paper 1).

Chapter 3 is an **overview of the aims, hypotheses, methodologies and studies** of the four main areas of research.

Chapter 4 details the **development of a novel voiding stimulation method**. The chapter includes a pilot study of 40 infants demonstrating the feasibility of the method, published in *Emergency Medicine Journal* (Paper 2).

Chapter 5 details the **randomised controlled trial comparing the new method to standard practice** for 354 infants. The trial compared rates of voiding, successful urine sample collection, sample contamination, and parent and clinician satisfaction. The chapter includes the trial protocol published in *BMJ Open* (Paper 3) and the trial results published in *The BMJ* (Paper 4).

Chapter 6 details the **health economic evaluation of the costs of urine sample collection**. The evaluation used a multi-stage probabilistic model to determine the costs and cost-effectiveness of current and new urine sample collection methods. The chapter includes the results published in *Archives of Disease of Childhood* (Paper 5).

Chapter 7 details the **qualitative study of the barriers and enablers to urine sample collection in Australian general practice**. The study includes semi-structured interviews with 25 doctors and nurses, and thematic analysis of data. The chapter includes the article in press accepted for publication in *British Journal of General Practice Open* (Paper 6).

Chapter 8 describes **knowledge translation** for the findings of the preceding studies. This includes authorship of updated statewide *Victorian Clinical Practice Guidelines for Paediatric UTI*, 2 clinical review articles published in *Archives of Disease of Childhood Education & Practice* and in the *British Journal of General Practice*, and 1 letter to the editor published in *Paediatrics and International Child Health* (Papers 7-9).

Chapters 9 is a **discussion** of the main findings of the research, strengths and limitations of findings, unanswered questions and areas for future research to address them. The implications of the research findings for clinical practice and guidelines are further described.

Chapter 10 summarises the work of the thesis, how the findings have informed clinical practice and guideline recommendations, and draws together **overall conclusions**.

Chapter 2 BACKGROUND

2.1 OVERVIEW

UTI IN YOUNG CHILDREN

The first section of this chapter provides an overview of early childhood UTI, and describes the clinical and laboratory features of this common infection. The aetiology, prevalence and potential complications of childhood UTI are also described. As many of the signs and symptoms of UTI in young children are non-specific, this section highlights why clinical diagnosis of UTI is unreliable and why a urine sample is necessary for evaluation.

SCREENING AND DIAGNOSTIC TESTS FOR CHILDHOOD UTI

The second section outlines the urine sample screening and diagnostic tests commonly used for childhood UTI, and how the progressively available results of urine sample testing are used to confirm or exclude the diagnosis. Controversies with test interpretation and the diagnostic approach are also explored.

URINE SAMPLE COLLECTION METHODS

The third section describes existing methods used to collect the required urine samples from children. It describes non-invasive and invasive methods, and the strengths and limitations of each method. International guideline recommendations and clinician preferences are compared. The rationale for improving collection methods for young pre-continent children is introduced.

COSTS OF URINE SAMPLE COLLECTION

The fourth section considers the costs of childhood UTI to the healthcare system, and why urine sample collection methods are an avenue for potential cost savings when evaluating childhood UTI.

CHILDHOOD UTI IN THE PRIMARY CARE SETTING

The fifth section considers how the nature of the primary care setting influences the evaluation and management of childhood UTI.

JUSTIFICATION FOR PRESENT RESEARCH

This background chapter therefore provides the rationale for developing a novel voiding stimulation method, for evaluating the costs of urine sample collection in young children, and exploring the barriers and enablers to urine sample collection that exist in the primary care context.

PAPER 1: CLINICAL REVIEW

A published clinical review (Paper 1) included in Appendix 11.1.1 forms part of this background chapter, and some text and figures from the published paper are included in this chapter.

1. **Kaufman J**, Temple-Smith M, Sanci L. Urinary tract infections in children: an overview of diagnosis and management. *BMJ Paediatrics Open* 2019;3:487. doi: 10.1136/bmjpo-2019-000487

The doctoral candidate was the lead author and was commissioned to write the manuscript, and was responsible for writing the first and final drafts of the manuscript.

Some text from an additional co-authored clinical review regarding the management of childhood constipation is included in this chapter, and the published paper is included in Appendix 11.1.5 of this thesis:

Waterham M, **Kaufman J**, Gibb S. Childhood constipation. *Australian Family Physician*. Vol. 46, No. 12, Dec 2017: 908-912. Available from: www.racgp.org.au/afp/2017/december/childhood-constipation/

2.2 URINARY TRACT INFECTION IN YOUNG CHILDREN

"UTI is a common bacterial infection causing illness in children. It may be difficult to recognise UTI in children because the presenting symptoms and/or signs are non-specific, particularly in younger children. Urine collection and interpretation of urine tests in children are not easy and therefore it may not always be possible to unequivocally confirm the diagnosis."

National Institute for Health and Care Excellence UK (2007) [6]

2.2.1 Fever in children: could it be UTI?

Fever (also known as pyrexia) is common in young children. Up to 40% of children under 5 years of age will have a febrile illness each year. [7] Concern about fever is common in parents, who may have misconceptions about fever, including that fever is a disease in itself rather than a sign of an underlying condition. [8] However fever may also be a sign of conditions which require medical attention and treatment, which to some degree validates such concerns. Fever is one of the most common reasons for a child to present for medical attention, and the second most common reason for a child to be admitted to hospital. [7 8]

The most common cause of fever in children is infection. [7 9] The majority of these cases will be viral infections, which are usually benign and self-limiting in nature. However a small minority will have serious bacterial infections, which require prompt identification and treatment. Approximately 10% of young febrile infants will have a serious bacterial infection such as meningitis, UTI or bacteraemia. [10] Clinicians evaluating children with fever aim to elucidate serious diagnoses to avoid potential morbidity and mortality, while limiting any unnecessary burden of investigation on the child and healthcare system.

Unfortunately many children with fever, particularly young pre-verbal children, have no identifiable source of infection despite careful clinical evaluation. Unexplained fever (also known as pyrexia of unknown origin, or PUO) is defined as a fever of 38 degrees celsius or greater in the absence of clinical signs or symptoms to suggest the source of fever. If no clear focus of fever is identified on history or examination, the child may require monitoring and time for the clinical picture to unfold and the focus to become evident, or further investigations to interrogate possible sources of infection.

UTI is an important and common bacterial infection of childhood which can cause fever. Clinicians seeing children with unexplained fever must therefore always consider whether UTI could be the culprit. Since the introduction of routine childhood immunisation with conjugated vaccines for Streptococcus pneumoniae and Neisseria meningitidis, UTI has become the most prevalent bacterial infection in children with unexplained fever. [11]

However as fever may be the only presenting feature of UTI in young children, [12] [13] it can be difficult to define and diagnose. The next sections explore the symptoms, signs and laboratory features of childhood UTI, and the difficulties commonly encountered when evaluating potential UTI in a young child.

2.2.2 Clinical features

The first step in the evaluation of unexplained fever or suspected UTI is a careful clinical history and examination. The history involves gathering subjective information from the parent or caregiver, and from an older child if age allows. The examination involves gathering objective information by observation and physical examination. Findings in younger children with UTI may be unclear compared to older children and adults. Therefore the history and examination will not confirm a UTI diagnosis, but will suggest which young children should be further evaluated.

The clinical features of childhood UTI are remarkably non-specific. [6] [14] These indistinct signs and symptoms are what makes the clinical diagnosis of UTI

highly unreliable. Young preverbal children provide a particular challenge, as they are not able to indicate or describe their symptoms. Children with UTI may appear quite well, or very unwell. [15] Fever is often present, and may be the only feature present, or the child may be afebrile. [16] Lethargy, poor feeding, vomiting, dehydration and irritability may be reported, [6 16] but these features are also present with many common and benign viral illnesses. Malodorous or discoloured urine may be noted by vigilant parents, [6 12] but may be obscured in nappy wearing children. This frequent lack of convincing clinical features means the potential diagnosis of UTI must be considered in all cases of unexplained fever in young children. [6 15 17 18]

Urinary tract infection can be categorised anatomically into upper tract UTI (pyelonephritis), and lower tract UTI (cystitis) (Figure 2). [6 12 14 19] Clinical signs and symptoms may correlate and suggest the site of infection. Upper tract UTI involves infection and inflammation in the kidney and ureters, leading typically to abdominal pain and loin tenderness with systemic features such as fever, malaise, lethargy, anorexia and vomiting. [12 19] Lower tract UTI refers to infection within the bladder and urethra, leading typically to more localised symptoms such as dysuria, urinary frequency and urgency, and lower abdominal or suprapubic pain. [12 19] However the classical signs and symptoms described above are often absent in the paediatric population. [16 20 21] Therefore in practice the clinical differentiation between upper and lower UTI is much less obvious in children. [12]

Figure 2: Urogenital system: upper and lower tract UTI

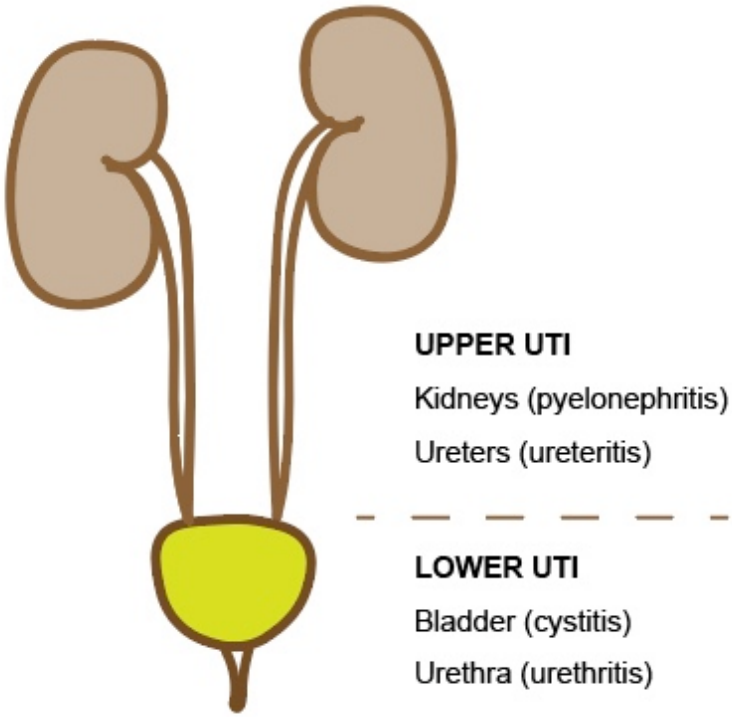


Image by the doctoral candidate, reproduced from Paper 1 (Kaufman et al, BMJ Paediatrics Open 2019) with publishers permission [20]

When clinical features from history or examination are suggestive of UTI, or another source of fever cannot be identified in the unwell child, the next step is collection of a urine sample. The urine sample can then be used for screening, and to confirm or exclude the UTI diagnosis. [6 15] Clinical practice guidelines accordingly recommend urine testing for potential UTI in all children with suggestive clinical features, or with persisting unexplained fever, to avoid either missed diagnosis or misdiagnosis. [6 15 16]

2.2.3 Laboratory features

The gold standard for the diagnosis of UTI is the presence of both clinical and laboratory features. Laboratory features includes the growth of a uropathogenic organism in sufficient quantity from an appropriate urine sample, accompanied by white blood cells suggesting active infection and

inflammation. [6 15 19 22 23] However all aspects of this definition require certain caveats in practice.

Bacteria in the urine is not sufficient to define UTI. Identifying the presence of a bacterial organism in the urine raises three possibilities. The first is that the organism is present in the urinary tract and is causing active infection, representing a UTI. The second is that the organism is present in the urinary tract but is not causing active infection, representing asymptomatic bacteriuria. [24 25] The third is that the sample accumulated some incidental skin flora during the collection process, representing contamination. [24 26] Therefore to diagnose a UTI, further evidence is required to demonstrate that the identified bacteria are actively causing infection in the host urinary system.

White blood cells in the urine (pyuria) may be present or absent with UTI, or present without UTI. Infection leads to local inflammation, and a host response including mobilising white blood cells to the urinary tract. [22] Pyuria, however, may be reduced in early infection, [16] or diminished in immunocompromised and neutropaenic patients. Pyuria may also be present due to a systemic response to infections outside the urinary tract, or introduced by sample contamination with mucosal secretions. [27] So while the presence of pyuria supports a diagnosis of UTI, it is not definitive, and its absence does not entirely exclude the possibility. [6 15 22 28 29]

It may not be possible in all circumstances to be conclusive with the UTI diagnosis when results are indeterminate. Nonetheless the clinician must make an initial decision based on the clinical history and examination regarding whether to collect a urine sample, with the laboratory features of urine testing used to advance the working diagnosis. Further detail regarding laboratory features, and their utility as screening and diagnostic tests for paediatric UTI, are explored in section 2.3.

2.2.4 The challenges of evaluating childhood UTI

The name UTI suggests, literally, that infection is present in the urinary tract, which would seem straightforward to identify. However as described above, the clinical and laboratory features of paediatric UTI may be indistinct. The clinical history may be vague and limited, the examination findings non-specific, and laboratory features of urine testing non-confirmatory. Defining and diagnosing UTI in a young child is therefore challenging.

In response to this diagnostic ambiguity, clinical decision making rules and a UTI risk calculator have been proposed to identify which febrile children require further investigation for UTI. [30-33] While the criteria in these rules are clinically sensible, and useful to identify some febrile young children at very low risk of UTI, they do not obviate the need for diagnostic confirmation with a urine sample for many children with suspected or potential UTI.

Collection of a urine sample allows identification of the biochemical signs of active infection and inflammation in the urinary tract, as well as accurate identification of the responsible organism to enable appropriate antibiotic therapy. The limitations of existing urine tests and the challenges of defining and diagnosing UTI are explored in more detail in section 2.3. What is clear, however, is that a clinical diagnosis is not sufficient, and a urine sample is absolutely required to properly evaluate UTI in young children.

2.2.5 Prevalence and epidemiology

UTI, as previously stated, is one of the commonest bacterial infections of childhood. [6] Overall it is reported in developed countries that around 1 in 10 girls and 1 in 30 boys will have had a urinary tract infection by the age of 16 years. [34] Among febrile infants, unwell children in general practice and older children with urinary symptoms, 3-9% will have a UTI in developed settings depending on the specific population, with a higher prevalence in developing settings. [1 13 35-37] As described in the published clinical review article (Paper 1) by the doctoral candidate, [20] prevalence varies with age, peaking in younger

infants, toddlers and teenagers. The reasons for these prevalence peaks and corresponding risk factors for UTI are described subsequently in section 2.2.7.

Identifying the presence of bacteria in a urine culture does not entirely correlate with true UTI prevalence, and clinical and laboratory definitions of UTI may vary between guidelines and settings. Therefore precisely estimating the true prevalence of childhood UTI is challenging. Nonetheless the following sub-sections summarise the reported UTI prevalence in populations of interest from the literature, with a focus on younger pre-continent children where this data is available.

2.2.5.1 Prevalence of childhood UTI in the hospital context

A commonly cited prevalence of UTI in febrile infants is 7%, based on a comprehensive 2008 meta-analysis by Shaikh et al. [1] However this meta-analysis used data nearly exclusively from studies in hospital emergency departments in the United States of America (US), which may limit generalisability to other contexts.

There is limited recent data from Australian and United Kingdom (UK) hospital settings. One recent Australian study found approximately 3% of febrile children younger than 5 years presenting to a tertiary hospital emergency department (ED) had a UTI. [38]

In hospital settings in developing countries, the prevalence of UTI in febrile young children ranges from 9-20%. [39 40]

2.2.5.2 Prevalence of childhood UTI in the primary care context

Childhood UTI is also common in the primary care context.

While there is limited data to suggest the exact prevalence of early childhood UTI in primary care, [41] recently published studies from the UK suggest a prevalence of 2-6% based on positive urine culture results. [42 43]

There is a lack of recent data for UTI prevalence in primary care settings from other countries.

2.2.5.3 Prevalence of childhood UTI in resource limited settings

Children in resource-limited settings may be at increased risk of UTI, and therefore suffer from a potentially serious bacterial infection in an environment with limited diagnostic and treatment resources.

Malnourishment in children can lead to immune deficiency and increased susceptibility to serious bacterial infections including UTI. [44] [45] Reported prevalence of UTI in malnourished children varies from 6-37%, although this variation may be in part due to differing study methods and confounders. [45-48] One small study of 17 malnourished and 2 control children found a significant increase in bacteriuria and UTI, which was proportionate to the severity of malnutrition. [44] Of concern, many of these UTIs are caused by treatment resistant organisms. One study in Tanzania found over 37% of gram-negative enteric bacteria on urine culture exhibited multi-drug resistance. [49]

Resource-limited settings also present specific clinical challenges. The reduced availability of appropriate health service resources in low and middle income countries increases the challenges of detecting and treating childhood UTI. Primary care for children in such settings may be very different to the well resourced clinics and hospitals of the developed world, and may lack the capacity to conduct laboratory tests or provide suitable treatments. In this equipment and expertise constrained context, urine sample collection may be limited to catching a spontaneously voided sample. UTI investigation may rely on clinical evaluation and dipstick urinalysis screening, or microscopy analysis without culture confirmation in some settings. [21] Increasing antibiotic resistance further increases the challenge of providing appropriate empiric therapy in resource-limited settings. [50]

Given UTI is one of the most common bacterial infections of childhood, with increased prevalence and antibiotic resistance in resource-limited settings, there is an urgent need for improvements to guidelines, investigations and

management of UTI suited specifically to low resource environments. Simple and inexpensive interventions, known as “frugal innovations”, have the potential to significantly improve healthcare in resource-limited settings and beyond. [51] Further research to develop pragmatic solutions to the common problems of UTI evaluation and diagnosis, including urine sample collection, could have significant benefits in such populations.

2.2.5.4 Prevalence of asymptomatic bacteriuria

Bacteria can be present in the urine without causing symptomatic infection of the urinary tract or kidneys, known as asymptomatic bacteriuria. While comprehensive data regarding its prevalence in childhood is lacking, asymptomatic bacteriuria is important as it may be misdiagnosed and treated unnecessarily as UTI.

In an unselected population of 3581 Swedish infants, 50 (1.4%) were found to have asymptomatic bacteriuria on one of three sampling occasions during their first year of life verified by suprapubic aspirate (the gold standard method of urine sample collection). Only 2 of the 50 infants with bacteriuria developed any signs of infection close to the time of detection. [25 52] A screening survey of older children aged 4 to 18 years in the UK showed a similar prevalence of asymptomatic bacteriuria, with an overall prevalence of 1.9% in 13,464 girls. [53]

Asymptomatic bacteriuria may be more prevalent in other populations. In separate prevalence studies of 1000 healthy Egyptian children aged 6-12yo and 196 Nigerian children with stable sickle cell anaemia, the prevalence of asymptomatic bacteriuria was 4-6%. [54 55]

Asymptomatic bacteriuria may affect UTI incidence estimates in the literature, and complicate the diagnostic evaluation of UTI, further highlighting the importance of reliable sample collection and culture results.

2.2.6 Aetiology

2.2.6.1 Susceptibility to UTI

Most UTIs arise from uropathogenic organisms originating from faecal flora. [56] These bacteria are present on the perineum and surrounding skin, and if able to ascend the urethra can enter the urinary tract and cause UTI. The flow of urine, bacterial virulence, host immune response and the specific pathogen all contribute to UTI defence and susceptibility. [57]

2.2.6.2 Urine flow

The flow of urine is the most important host defence against UTI, [57] as urinary flow physically flushes and expels potential pathogens from the urinary tract. Urine is supposed to flow unidirectionally from the kidneys to the bladder, with near complete emptying of the urinary reservoir through the urethra on bladder voiding. Disruption of this normal flow pattern can include retrograde urinary flow, urinary stasis and incomplete bladder emptying. [56]

Accordingly, children with impaired urinary flow are more susceptible to UTI, as pathogens have increased opportunities to ascend the urinary tract and establish active infection. Urinary flow can be affected by either structural urogenital tract anomalies or functional voiding disturbances, which are described in further detail in section 2.2.7 outlining the clinical risk factors for UTI.

2.2.6.3 Bacterial virulence

Some uropathogenic bacteria have developed specific strategies to attach themselves to the uroepithelial cells of the urinary tract. [57] For example, uropathogenic strains of Escherichia coli (E.coli) have specialised fimbriae which are long thin appendages that can specifically attach to the uroepithelium (Figure 3). This enables these bacteria to avoid the rapid and unceremonious expulsion which occurs with urine voiding, allowing these bacteria to hold on, establish infection and replicate in the urinary tract. [57]

2.2.6.4 Host immune response

The host response to infections, including UTI, consists of innate and acquired components of the host immune system. [57] Innate immunity provides an immediate response and resistance against pathogens, including intrinsic defences in the uroepithelium such as inflammatory cytokines, complement activation, and recruitment of phagocytes. [56] Acquired immunity provides defence against recurrent infections, however as children with B and T cell immunodeficiencies are not dramatically susceptible to UTI, the acquired immune system does not appear to be the major player in protection against UTI. [57]

2.2.6.5 Pathogens causing childhood UTI

Most paediatric UTI is caused by gram-negative coliform bacteria originating from faecal flora. [56] E.coli is the most common uropathogenic organism (Figure 3), responsible for up to 90% of childhood UTIs. [14 34 43 58 59]

Figure 3: Escherichia coli with fimbriae

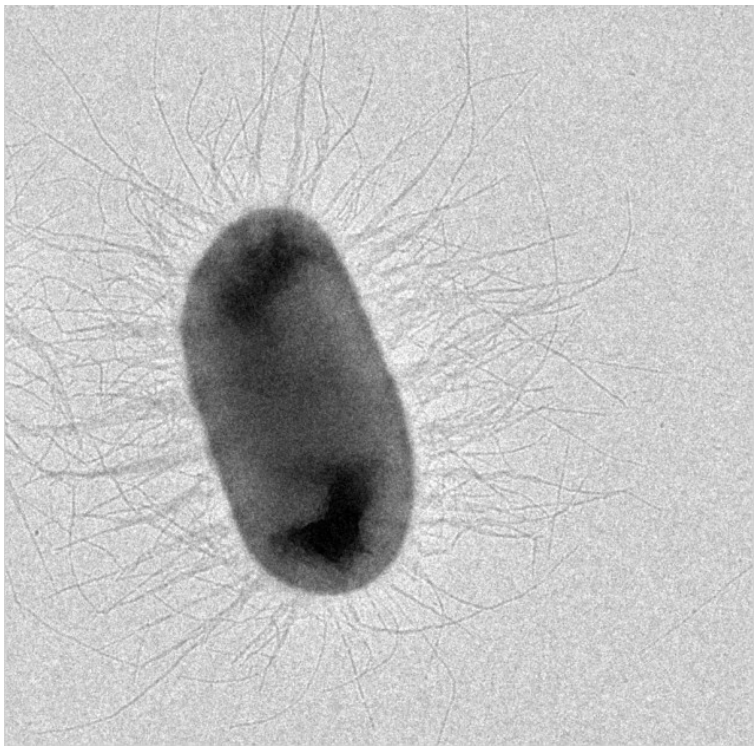


Image provided by A/Prof Esther Bullitt, Brandeis University, reproduced with permission.

Other described bacterial uropathogens include Klebsiella, Proteus, Citrobacter, Enterobacter, Enterococcus, Serratia, Pseudomonas, Morganella, Group B Streptococcus, Haemophilus influenza and Staphylococcus saprophyticus species. [14 29 43 58-60]

The overwhelming majority of paediatric UTIs have a bacterial aetiology, but other types of pathogens can infect and invade the urinary tract. Candida albicans funguria may occur after antibiotic or immunosuppressive therapies. [14] Viruses such as BK virus, cytomegalovirus (CMV) and adenovirus can cause haemorrhagic cystitis in immunocompromised patients, particularly after stem cell and solid organ transplantation. [61] However fungal and viral UTI is very rare in children who are not immunosuppressed.

The growth of multiple bacterial species on culture (known as “mixed growth”), or organisms known to be non-pathogenic skin commensals (such as Staphylococcus epidermidis and Staphylococcus aureus species), suggests sample contamination. [19] Contamination can occur when incidental organisms in the urethra and perigenital skin are flushed with voiding into the collected urine sample, or inadvertently enter the specimen jar from the hands of the person collecting the sample or from the surrounding environment. Contamination corrupts interpretation of the test result. Sample contamination and its significance in evaluating UTI is discussed in further detail subsequently in section 2.4.4.

Paediatric UTI shows significant inter-region variability in patterns of aetiology and also antibiotic sensitivity. [58] Knowledge of the local aetiologies and antimicrobiogram is therefore essential to guide empiric UTI therapy, as laboratory culture confirmation of the organism and antibiotic sensitivities will not be available to the clinician for 24-48 hours. Published international guidelines may not reflect local sensitivity patterns, [23] which can lead to overly narrow or broad empiric treatment recommendations, and makes empiric treatment selection an increasing challenge in an era of evolving antibiotic sensitivities and resistance.

As immunisation has reduced the incidence of other serious bacterial infections of childhood from Haemophilus influenza B and Streptococcus pneumoniae species, [10] UTI has become an even more common cause of serious and occult infection in young children. Untreated UTI has the potential for bacteraemic spread and further complications. [15 35] Therefore confirmation of UTI aetiology and antibiotic sensitivities with laboratory culture is important to guide targeted therapy. Culture confirmation of aetiology and sensitivities is dependent on the collection of an appropriate urine sample.

2.2.6.6 Antibiotic resistance in childhood UTI

Antibiotic resistance is an increasing global concern, for many types of infection, including UTI. Worldwide, there is an increasing appreciation for the resistance of common uropathogens such as E.coli to recommended first line empiric antibiotics. [50 58 62]

The usual mechanism for this increasing antibiotic resistance is through the acquisition of enhanced beta lactamase enzyme properties. Some gram negative uropathogens are able to inactivate beta-lactam ring antibiotics such as penicillin and early generation cephalosporins with inherent beta-lactamase enzymes. However some have acquired further multi-drug resistant properties through evolution of these enzymes to include the ability to hydrolyse and inactivate extended spectrum cephalosporins and carbapenem antibiotics. [63] Such organisms are known as Extended Spectrum Beta Lactamase (ESBL) organisms.

Trimethoprim, trimethoprim with sulfamethoxazole, and cefalexin were the previously recommended empiric oral antibiotics for paediatric UTI in 2015 Australian guidelines, [64] with more recent guidelines recommending only cefalexin. [16] UK Guidelines recommend for children less than 3 months the use of an oral antibiotic with low resistance patterns such as trimethoprim or nitrofurantoin, and for children older than 3 months that the choice of antibiotics is guided by local recommendations, but that nitrofurantoin, cefalexin or amoxicillin may be suitable. [65] US Guidelines recommend choosing antibiotics based on local sensitivity patterns and to adjust these

once sensitivity patterns of the isolated uropathogen are available, but acknowledge that "basing the choice of an initial antimicrobial agent on local sensitivity patterns can be difficult because applicable information may not be available". [23] However an increasing prevalence of UTIs resistant to these agents is apparent in Australia, the UK and US. [50 59 66] While ESBL organisms where once seen primarily in the hospital setting, ESBL UTI incidence in the community is also rising. [63]

The pooled prevalence of resistant E.coli organisms in childhood UTI is also significantly higher in non Organisation for Economic Co-operation and Development (OECD) countries than OECD countries for all antibiotics. [50] In some settings exceptionally high rates of 64-97% of E.coli are resistant to first line oral antibiotic therapies such as cotrimoxazole, and up to 32% resistant to first line intravenous antibiotic therapy such as gentamicin. [40 67] This may be due to widespread use of broad spectrum antibiotics in the community generally, or because urine sample collection and laboratory processing may not be possible in resource-limited settings. [21] Inadequate sample collection and processing leads to untargeted UTI therapy.

Increasing antibiotic resistance of E.coli and other organisms is making empiric therapy challenging. Infections with antibiotic resistant organisms are known to be associated with higher morbidity, mortality and health-care costs. [62 68] Accurate and timely diagnosis of UTI with culture confirmation is therefore vital to reduce inappropriate antibiotic prescription for misdiagnosed UTI or resistant UTI, and combat the increasing antibiotic resistance of uropathogenic bacteria.

2.2.7 Risk factors

Certain groups of young children are reported to be at increased risk of UTI. As described previously in this chapter and published review article (Paper 1), the prevalence of childhood UTI peaks in female and uncircumcised male infants, toddlers and sexually active adolescents. [20] The clinical risk factors

underlying these prevalence peaks are described in this section, with a focus on the young pre-continent children who are central to this doctoral research.

2.2.7.1 Risk factors for UTI in young pre-continent children

Younger pre-continent children, with a high concentration of bacterial skin flora under the infant nappy area, and an immature immune system in the first six months of life, generally have a higher risk of UTI. Female infants and uncircumcised male infants, in particular, are known to be at increased risk of UTI. [1 13 35-37 69] This is understandable given the anatomical differences of these groups. Females have a shorter urethral distance, giving bacteria on the perigenital skin a shorter path to ascend into the urinary tract. Uncircumcised males have an accumulation of bacteria under the foreskin, [69] and these bacteria on the prepuce and glans penis can enter the urinary tract via the urethra and cause UTI.

However it is possible that some of the reported increased prevalence in these groups may be due in fact to false positive results rather than true UTIs. In young female and uncircumcised male infants it may be more difficult to collect a urine sample without inadvertent sample contamination. Ballooning of the foreskin and flushing of the vagina with urine voiding is seen on fluoroscopic micturating cystourethrograms (MCUGs), demonstrating a normal physiological phenomenon which may wash incidental skin flora into the sample. [26] Catheterisation may be more technically challenging, and clean catch and bag samples may be more prone to contamination. These collection challenges are discussed further in section 2.4.

Some American studies reporting UTI prevalence in infancy by race found an increased incidence in white compared to African American infants, [1] while others did not. [36] It is a possibility that racial differences in UTI incidence within countries could be due to difference in circumcision rates amongst boys in certain groups, [1] or ascertainment bias in these studies.

2.2.7.2 Risk factors for UTI in older continent children

Other risk factors in older children can also increase susceptibility to paediatric UTI. Bladder and bowel dysfunction are known to increase the risk of UTI, [70 71] by contributing to urinary stasis. Uropathogens then have more time and increased opportunity to become established UTI. This includes common conditions such as functional constipation, and during toddler toilet training which can lead to voluntary holding. [57] Structural renal abnormalities or neurogenic bladder may also impede urine flow, leading to delayed flushing of bacteria via the bladder and an increased reservoir for bacterial incubation. [19 35] Immunocompromise may increase general susceptibility to infection. Sexual activity can disrupt skin flora in adolescent females when bacteria near the urethral orifice are disrupted. [1]

2.2.7.3 Risk factors for recurrent or complicated UTI

Certain risk factors may increase susceptibility to recurrent UTI, or complicated and severe infections with increased morbidity. Structural and functional urogenital abnormalities affecting urinary flow such as bladder-bowel dysfunction and severe vesicoureteral reflux, as well as atypical non-E.coli uropathogens, have all been demonstrated to increase the risk of UTI and UTI sequalae including renal scarring. [56 72]

2.2.7.4 Structural urinary tract anomalies

Structural (anatomical) abnormalities of the urinary tract may alter the flow of urine, which is formed in the kidneys and travels unidirectionally via the ureters and bladder to be expelled from the urethra. Urinary stasis provides a reservoir for uropathogens, allowing them to proliferate internally rather than being flushed externally. Structural urinary tract abnormalities include obstructing posterior urethral valves in boys and pelviureteric junction obstruction in boys and girls.

2.2.7.5 Vesicoureteral reflux

Vesicoureteral reflux (VUR), the retrograde flow of urine from the bladder to the kidney, was historically thought to significantly predispose children to recurrent UTI and renal scarring. VUR however occurs along a spectrum of

severity, graded 1 (mild) to 5 (severe) with increasing dilatation of the urinary collecting system. During the 1980s to the early 2000s, while the view prevailed that all VUR was significant, many children underwent invasive imaging such as MCUG tests to identify VUR. Those with VUR subsequently received antibiotic prophylaxis to reduce the risk of further UTI until there was natural resolution of VUR with time, or surgical correction to correct high grade reflux. [15] The aim of the antibiotic prophylaxis was to prevent renal scarring as a consequence of recurrent UTI in the presence of VUR.

However children with lower grade reflux are the least likely to develop renal scarring, and the most likely to see the reflux naturally resolve with time. [73] Routine antenatal ultrasound also now identifies many cases of in-utero fetal hydronephrosis (enlargement or dilation of the renal pelvis and calyces) and structural renal abnormalities, with the subsequent scarring sometimes seen on postnatal follow-up imaging not always associated with UTI events. It is therefore proposed that congenital renal dysplasia from reflux, rather than acquired damage from milder VUR and subsequent UTI, causes this scarring that was previously blamed on postnatal UTI.

Severe grade 4-5 VUR includes gross dilatation of the urine collecting system, which is less likely to spontaneously resolve than lower grade VUR. [74] These children may also be more susceptible to renal damage due to a combination of both congenital renal dysplasia from reflux and acquired UTI related scarring. Therefore children with higher grade reflux may benefit from greater vigilance to preserve renal parenchyma from damage from UTI, to prevent potential long term renal morbidity. Prompt urine sample collection and empiric therapy is indicated when UTI is a possible diagnosis for these children.

Because VUR was thought to be associated with increased risk of recurrent UTI with associated sequelae and morbidity, [75] historical prescription of antibiotic prophylaxis to prevent recurrent UTI was common for these children. However it is now known that antibiotic prophylaxis in this context has limited

effectiveness in preventing renal scarring, which must be balanced against the risk of encouraging antimicrobial resistance. [70]

Therefore guideline recommendations are evolving, with less routine imaging to identify VUR in all children with first UTI, and more targeted and risk stratified imaging now recommended. [65] International guideline recommendations for imaging after childhood UTI are summarised in Table 3 of the published clinical review by the doctoral candidate (Paper 1, Appendix 11.1.1). [20] Ultrasound is the preferred initial investigation, with further imaging reserved for those with positive findings.

For children with known VUR there should still be a low threshold to evaluate early for potential UTI in cases of febrile illness, including appropriate urine sample collection, due to the increased risk of UTI compared to the general population. [76]

2.2.7.6 Functional urinary tract disturbance

Functional disturbances to the urinary tract and bladder function include neurogenic bladder, dysfunctional voiding and constipation. While the urinary tract is structurally normal, these children have abnormal flow of urine, leading to urinary stasis and incomplete bladder emptying, [57] which in turn predisposes to UTI.

There is increasing recognition of bladder-bowel dysfunction as an important risk factor for childhood UTI in young continent children. [56 57 76] Younger pre-continent children void urine freely. Both constipation and behavioural withholding, which often occur around the time of toddler toilet training, lead to disordered and dysfunctional voiding, with resultant increased urinary residual volumes and urinary stasis.

Constipation affects 3-30% of children worldwide depending on setting, [77] and is a common and important cause of bladder-bowel dysfunction in young children. Therefore addressing constipation is a simple but important strategy to reduce the risk of childhood UTI. The evaluation and management of

childhood constipation is described in detail in a co-authored clinical review article included in Appendix 11.1.5. [77]

2.2.7.7 Uropathogenic organisms

UTI aetiology may also have implications for UTI complications. Most childhood UTI is caused by E.coli, [58 59 73] but UTIs caused by non-E.coli organisms have been shown to be associated with an increased risk of renal scarring. [72] Therefore some clinical practice guidelines recommend non-E.coli UTI be classified as “atypical UTI”, with corresponding implications for specific imaging and follow-up. [20] Reliable urine sample collection prior to initiation of antibiotic therapy is therefore important to accurately identify the uropathogenic culprit on culture.

2.2.8 Morbidity and mortality

The aim of timely and accurate diagnosis of childhood UTI is to allow prompt and targeted treatment, to reduce morbidity and mortality. Acute UTI can vary in its severity, encompassing the full clinical spectrum from mild dysuria in an otherwise well child through to life-threatening urosepsis. While serious infection is less common, it can and does occur particularly in younger children. [78] UTI is recognised in the literature as a frequent cause of occult and serious bacterial infection in infants, [10 15] though mortality is thankfully very rare. Medium term morbidity includes recurrent infection and permanent renal scarring, which has the potential in the most severe cases to cause long term morbidity with hypertension and chronic renal failure.

2.2.8.1 Short term morbidity within the renal system

Short term morbidity from UTI includes serious infection locally within the urogenital system. Infection within the lower renal system (cystitis) alone is unlikely to cause systemic illness and significant complications.

Infection of the upper renal system (pyelonephritis) may lead to associated systemic symptoms and further local complications, [19] including renal corticomedullary and perinephric abscess formation. Suppurative

complications of UTI are more common in adults and patients with structural urological abnormalities, and are fortunately uncommon in otherwise healthy children. [79]

2.2.8.2 Short term morbidity outside the renal system

Serious bacterial infection from UTI can also migrate outside the urogenital system. Uropathogenic organisms can enter the bloodstream (bacteraemia), which can lead to more widespread infection (urosepsis) including brain and spinal cord involvement (meningitis).

The incidence of bacteraemic UTI has been best studied in the infant population, as this population is most likely to have a blood culture collected during episodes of febrile illness. The reported incidence of bacteraemic UTI in the infant population varies from 3-17% in the literature. [10 80-82]

Bacteraemia can then lead to urosepsis. While the overall incidence of severe paediatric sepsis is low in developed countries, from population based incidence studies, approximately 4% of paediatric sepsis cases have a documented genitourinary source of infection (urosepsis). [78]

Meningitis can occur with seeding of uropathogenic organisms from the blood stream to the cerebrospinal fluid (CSF). Typical empiric antibiotic therapy for UTI may have poor CSF penetration and inadequate treatment duration for bacterial meningitis. [83] Therefore identification of co-existing meningitis with UTI has important treatment implications, as partially treated meningitis can have severe and potentially long term consequences. [84] Historically the incidence of co-existing UTI and meningitis was thought to be as high as 19% in infants, [85] although these studies are limited by small sample sizes and variable definitions of UTI. The incidence of meningitis arising from UTI is more recently reported as 0-2% in the neonatal and infant population, [84 86-90] and up to 4.7% arising from bacteraemic UTI. [80] A local 9 year analysis of 735 cases of children 0-16 years of age with paired urine and CSF samples found no cases of culture proven co-existing meningitis with UTI outside the neonatal age range. [84] A more selective approach to lumbar puncture may

therefore be more appropriate than universal application for older infants with UTI. While meningitis arising from UTI is very rare outside early infancy, [82 84 91] the consequences of inadequately treated meningitis at any age can be devastating, and vigilance for concurrent neonatal UTI and meningitis is warranted.

While younger children, and particularly neonates, are the group most vulnerable to acute UTI complications such as urosepsis, they are also the group in which the clinical signs of UTI are the least distinct, and in whom collection of a urine sample to evaluate UTI is the most challenging.

2.2.8.3 Mortality from UTI

Mortality from UTI is thankfully uncommon. Population based studies of paediatric sepsis in North America suggest an overall sepsis incidence of 0.56 per 1,000 per year, of which 4.1% arise from UTI, with a urosepsis mortality rate of 3.7%. [78 92] In a retrospective review from 20 US hospitals of 1842 infants aged 29-60 days presenting to the ED with UTI and fever, there were 2 deaths (0.1%). [82] Although UTI mortality is uncommon, every case is significant.

2.2.8.4 Medium term morbidity from UTI: recurrent infection

It is known that children who have had a first UTI are at increased risk of recurrent UTI. One systematic review including 4891 children from 33 studies found an overall incidence of UTI recurrence per year of 6-8%. [93] In a large cohort study of 74947 children in primary care paediatric practices aged less than 6 years old, 12% of children with a UTI had recurrent infection per year. [94] Hospital based studies of recurrence after uncomplicated UTI have shown a similar recurrence rate of 17% over a 2 year follow-up period. [75]

Vesicoureteric reflux (VUR) and bladder-bowel dysfunction (BBD) are known risk factors for recurrent UTI. Children with UTI and VUR have recurrence rates as high as 20-25%, [75 76] children with UTI and BBD have recurrence rates as high as 35%. [76] These effects appear cumulative, with 51% of children with both VUR and BBD experiencing recurrent UTI. [76] Children with

other conditions impairing voiding and the flow of urine also have a significantly increased risk of recurrent UTI. [20] This includes neurological conditions affecting bladder function and anatomical urogenital tract anomalies affecting urine flow.

Recurrent UTI is thought to be important as it may increase the risk of renal scarring and subsequent complications, though the degree to which this is the case is controversial.

2.2.8.5 Medium term morbidity from UTI: renal scarring

Renal scarring and an associated consequential renal morbidity have historically been significant concerns in the context of paediatric UTI. Though minor scarring is not uncommon after UTI, emerging evidence suggests that longer term sequelae of scarring is less common than previously thought. A comprehensive discussion of this topic is beyond the scope of this thesis, but a brief summary is described below and in the subsequent section.

Renal scarring acquired from UTI in childhood is not uncommon. A 2010 systematic review found 15% of children with UTI had evidence of renal scarring on follow-up DMSA scan, with an increased likelihood in the presence of vesicoureteral reflux. [93] A subsequent meta-analysis of 9 cohort studies found risk factors for developing renal scarring included abnormal renal ultrasound imaging, fever >39 degrees celsius, and a non-E.coli uropathogen aetiology. [72] Delayed treatment of paediatric UTI has also been shown to increase the risk of developing renal scarring. [95 96] While paediatric UTI is therefore a common cause of acquired renal scarring, severe scarring is uncommon, and it is unclear whether minor scarring actually predisposes children to an increased risk of further renal morbidity.

Severe short-term renal morbidity from scarring following childhood UTI is rare but has been reported in the literature, including cases of severe hypertension requiring unilateral nephrectomy. [96]

However it is now contested amongst experts and in the literature whether minor renal scarring after UTI matters in the longer term. [96] [97]

2.2.8.6 Long term morbidity from UTI: permanent renal impairment

Childhood renal scarring has been proposed to predispose to longer term renal morbidity including hypertension, pre-eclampsia, chronic kidney disease (CKD) and end-stage renal failure decades later in life. However studies of long term morbidity following UTI have shown inconsistent results, with more recent data suggesting the risks are lower than previously thought.

Historical data from earlier studies suggested these sequalae were not uncommon, leading to aggressive imaging guidelines to identify children at risk of such morbidity after UTI. One smaller study with 27 year follow-up of 30 patients with focal scarring following pyelonephritis from the 1950s and 1960s found that one third had suffered renal morbidity including hypertension, renal failure and renal surgery. [98] However these results have not been confirmed in more recent studies. [99]

Other cohort studies have found preserved renal function by measured glomerular filtration rate (GFR) and a low risk of hypertension two decades after childhood UTI both with and without renal scarring. [100] [101] However the individually scarred kidneys did show a reduction in GFR, and there were few patients with bilaterally scarred kidneys, so the longer term prognosis could be compromised for patients with bilateral scarring. A 2012 review of 23 publications found impaired renal function associated with UTI will be evident at first presentation for most children, with only 0.4% demonstrating a decline on follow-up, and a low risk of subsequent hypertension. [102] Another study of 366 CKD patients found 3% had a history of UTI in childhood, all of whom demonstrated renal abnormalities evident on renal ultrasonography, and recurrent UTI was possibly the cause of CKD in only 0.3%. [97]

It is now generally accepted that most children at risk of significant renal complications following UTI are likely to have structural abnormalities that can be identified on ultrasound imaging, [97] such as congenital renal tract

anomalies or urinary obstruction, [103] and that some renal scarring identified after UTI may in fact be congenitally acquired. The proposed causal link between childhood UTI, renal scarring and adult CKD therefore has not been conclusively demonstrated, although longer term cohort and retrospective studies do have limitations. [103] Nonetheless, while the risk of long-term renal morbidity from UTI and severe renal scarring may be lower than previously thought for most children, the consequences for the individual are severe should it occur.

2.2.9 Summary of childhood UTI

UTI is a common childhood bacterial infection. Clinical signs and symptoms can be non-specific, especially in younger children, making it an important diagnosis to consider in all febrile infants and toddlers. In practical terms, childhood UTI can be elusive. It is therefore omnipresent as the potential culprit amongst the many children with unexplained fever encountered by clinicians in general practice, emergency and hospital settings.

Timely and accurate diagnosis of UTI is important because misdiagnosis, missed diagnosis and delayed treatment can have undesirable consequences. Younger children and particularly neonates are the group most vulnerable to acute complications. They are also the group in which the clinical signs of UTI are the least specific, and the group where collecting a urine sample to evaluate UTI is the most challenging.

Most children with UTI make a full recovery. However serious short-term morbidity such as urosepsis and meningitis, and longer-term morbidity such as renal scarring and renal impairment, can occur. While these occur in only a low proportion of cases, the high prevalence of UTI in childhood means that the absolute rate of these complications is not insignificant.

When childhood UTI is the possible cause of a febrile illness, clinical diagnosis is highly unreliable. Therefore a urine sample must be collected to confirm or exclude the diagnosis with further testing.

2.3 SCREENING AND DIAGNOSTIC TESTS FOR CHILDHOOD UTI

"Urine should be collected and analysed by dipstick or microscopy to identify children in whom UTI is very likely, and if urinalysis is abnormal, by urine culture to obtain a definitive diagnosis."

Italian Society of Pediatric Nephrology (2019) [104]

Evaluating childhood UTI based on clinical assessment alone has been described as navigating "murky waters", [105] and international guidelines are clear that when childhood UTI is possible or suspected, a urine sample is required to confirm or exclude the diagnosis. [6 15 18] Once obtained, the sample can be inspected and used for immediate bedside dipstick screening, which provides supporting evidence to guide initial clinical management. Samples are then sent to the laboratory for microscopy and culture confirmation, to confirm the diagnosis and guide targeted antibiotic therapy. While culture confirmation with supporting evidence of active infection is regarded as the gold standard for UTI diagnosis, [22] precise diagnostic definitions are debated in the literature.

2.3.1 Screening tests: visual appearance, dipstick, microscopy

2.3.1.1 Visual appearance

Historically, doctors used the smell, colour and taste of a patient's urine to diagnose various diseases including UTI. [27] The English physician Thomas Willis observed that the urine of diabetic patients was "wonderfully sweet, as if imbued with honey or sugar". [106] Hippocrates described turbid urine as a feature of a disease of the kidney similar to cystitis. [107] Clinicians can perhaps be grateful they no longer need rely on such intimate urine sample testing to diagnose these conditions. The visual appearance and odour of the urine may suggest changes in the urine due to infection, which might be noted on inspection of the sample by the clinician or parent. However the colour and smell of urine can change in the presence of dehydration and other circumstances, so are not considered reliable diagnostic indicators of UTI.

2.3.1.2 Dipstick

Urine dipstick testing (also known as a full ward test) is a fast and cheap bedside screening tool, able to detect certain substances in the urine which may indicate the presence of UTI. [108] The dipstick is a test strip with various chemical reagent squares, which change colour in the presence of specific substrates. This includes blood, protein, nitrites (produced by bacterial reduction of urinary nitrates), and leucocyte esterase (an enzyme present in white blood cells). [109] Blood and protein are not considered to be reliable markers of UTI. [6 109]

Urinary nitrites are produced by most gram-negative enteric bacteria in the urine, which convert dietary nitrates into urinary nitrite. [15 27] Nitrite testing on dipstick is highly specific for UTI, but not very sensitive. Nitrites take up to 4 hours to develop in the urine, [27 110] so they may be flushed out of the bladder by the frequent voiding of young children. [15] Additionally, not all urinary pathogens produce nitrites. The most common uropathogenic organism in childhood UTI is E.coli, [111] which does produce nitrites, but other uropathogenic organisms including Klebsiella and Enterococcus species do not. [27] Therefore the absence of nitrites on dipstick does not exclude UTI. [15 27 112] The sensitivity and specificity of nitrite dipstick testing for paediatric UTI has been shown to vary between 49% and 98% from a meta-analysis of 46 previous studies. [113]

Leucocytes (white blood cells) commonly appear in the urine as a response to infection in the urinary tract, but detection of leucocytes in the urine is not specific for UTI. Sterile pyuria can occur with flushing of the skin or other infections, so the presence of leucocyte esterase alone on dipstick does not confirm UTI. [15 27] Testing for leucocytes is also not fully sensitive for UTI, and pyuria is absent in over 10% of children with culture confirmed UTI. [29] Leucocytes may not be present in significant numbers in early infection or neutropaenic patients. [60] Certain uropathogens have lower rates of pyuria, being significantly lower in Klebsiella, Enterococcus and Pseudomonas UTI compared to E.coli UTI. [29] Leucocyte esterase on dipstick may not be detected at lower white blood cell counts in the urine. [64 113]

In practice, the dipstick result for leucocyte esterase and nitrites are commonly interpreted in combination. [109] There is significant heterogeneity between studies regarding the sensitivity and specificity of combined urine dipstick tests for paediatric UTI. [109] In the literature the sensitivity of this combination for detecting UTI ranges from approximately 30 to 90%, while the specificity is higher at >90% in most studies. [109] So while UTI is less likely if the dipstick test is negative and more likely if it is positive for both leucocyte esterase and nitrites, false negative results are possible. This may occur in early infection with a non-nitrite producing uropathogen. False positives are also possible due to pyuria for other reasons and the general limitations of the test. The results of dipstick testing have also been shown to be less reliable in younger children, [112] which is frequently the population with the least clear clinical presentation and most at risk of morbidity from missed UTI.

In the absence of more accurate screening biomarkers, dipstick testing can at least supplement the initial clinical assessment to suggest whether UTI is more likely or less likely, and guide immediate management. If UTI is suspected on balance, empiric antibiotic therapy can be commenced while waiting for culture confirmation. If UTI is less likely and the child is not too unwell, the clinician can focus their evaluation on alternate diagnoses, or allow time for the clinical picture to unfold with a planned review. If there is a strong clinical suspicion of UTI however, a negative urine dipstick test may not be sufficiently reassuring to exclude the diagnosis. [105]

Further research is needed to define the accuracy of urine dipstick testing to screen and diagnose UTI in the paediatric population. [6] Guidelines therefore do not recommend that dipstick results be used to confirm a UTI diagnosis. [6 15 18 19 60] If UTI is suspected from dipstick screening, a reliable specimen should be sent for microscopy and culture in the laboratory to confirm the diagnosis. [6 15 23 105] Laboratory results for microscopy and culture may not be available for 24-48 hours, but can be used subsequently for diagnostic confirmation and to refine the treatment plan.

2.3.1.3 Microscopy

After bedside screening by dipstick, the urine sample can be sent to the laboratory for further testing. The laboratory testing is a two-stage process, consisting of initial microscopy screening to identify the presence of bacteria and white cells, with subsequent diagnostic confirmation with culture of the uropathogen and evaluation of antimicrobial sensitivities.

Bacteria can be visualised under microscope inspection, usually following gram staining of the specimen. Summary estimates from meta-analysis for the sensitivity and specificity of bacteria on microscopy for paediatric UTI were 91% and 96% for gram-stained bacteria from 17 studies, and 88% and 92% for unstained bacteria from 22 studies. [113] The presence of bacteria, however, can be due to asymptomatic bacteriuria or contamination from incidental skin flora, [6 25] so is not sufficient to confirm a UTI diagnosis.

White blood cells in the urine can also be identified and quantified in the laboratory. This can be performed manually under the microscope by a laboratory scientist or technician, or with an automated chemistry analyser. A cut-off point of 10 white blood cells per high-power field or per cubic millimetre is most commonly used in the literature to define pyuria. [109] Sensitivity and specificity for urine white cells in UTI was found to be 74% and 85% on meta-analysis of 49 studies. [113] A recent study found that pyuria (defined as ≥5 white blood cells per high-powered field or ≥10 white blood cells per cubic millimetre) was present in 87% and absent in 13% of paediatric UTI in a retrospective analysis of 1181 children with UTI in an American paediatric ED. [29]

Urine microscopy can also identify and quantify the presence of squamous cells in the urine. Squamous cells from the epithelial skin layer indicate that the urine or specimen jar has had significant contact with the skin, suggesting a poorly collected sample, and an increased risk of sample contamination with incidental skin flora bacteria. Contamination is a significant issue in urine sample collection in young children and is discussed in more detail subsequently in section 2.4.4.

Microscopic examination of the urine for bacteria and leucocytes is more time-consuming and labour intensive than performing a dipstick test, [109] and may not be readily available in all circumstances. [113] In the ED and hospital setting, where laboratory services are available on-site and results are readily available, microscopy can provide a useful rapid adjunct to the dipstick screening for clinicians. In most hospitals the laboratory microscopy services will be available until approximately midnight, so some samples collected in the early hours of the morning will be refrigerated for processing during business hours. [114] In the primary care setting all urine samples need to be sent to a laboratory for processing, and samples may not be collected until after the clinical consultation. In this context, microscopy results will not be available for initial screening and management decisions. Delayed microscopy results can still be useful to supplement the overall clinical and diagnostic picture, particularly when the culture is contaminated.

Therefore while microscopy results can supplement dipstick results for screening, the subsequent culture result is required for diagnostic confirmation. However in resource-limited settings and developing countries where bacterial culture is not available, the diagnosis may need to be made based on clinical signs and urine microscopy. [21]

2.3.2 Diagnostic tests: urine culture

Urine culture is the gold standard for confirming a suspected UTI diagnosis, in the presence of pyuria and a correlating clinical picture suggesting active infection. [15] [111] All major international guidelines recommend that urine culture is required to diagnose UTI in young children. [6] [12] [15] [18] [19] [60] This is because there is no rapid screening test sensitive enough to detect all childhood UTI. [114]

2.3.2.1 Culture process

There are two commonly used methods for performing the urine culture. The standard method involves streaking urine over an enrichment media and observing for bacterial growth. [109] More recently the dipslide method has been

described, involving submerging the dipslide (a miniature culture plate) into urine. [109] Culture results are considered positive if there is growth of a bacterial organism on culture medium at a sufficient quantity. Culture of common uropathogenic organisms (e.g E.coli, Klebsiella, Enterobacter, Enterococcus) supports the diagnosis of UTI. [60] Growth of non-pathogenic organisms in an otherwise well child who is not immunocompromised, or mixed growth of multiple organisms, suggests sample contamination.

Laboratory culture also provides the clinician with the antibiotic sensitivities of any organisms that are identified. The desired antibiotics can be applied to an agar plate inoculated with the cultured organism, and growth inhibition of the organism can be observed and quantified. In an era of increasing antimicrobial resistance of uropathogens to empiric therapy, these results are increasingly important to accurately target antibiotic therapy. An appropriately collected sample free from contamination is required to accurately identify the antibiotic sensitivities.

2.3.2.2 Concentration of bacterial growth

After laboratory processing, bacterial culture growths are reported in bacterial colony counts known as colony forming units (CFU). Higher CFU represents a higher concentration of bacteria in the specimen. But what CFU counts are significant? A cutoff value of 100,000 colonies per ml (10^5 cfu/ml or 10^8 cfu/L) is regarded by many guidelines as sufficient growth to represent true UTI. [6 18 19 60] This cutoff was established historically from a seminal study of pregnant women in the 1950s, as 10^5 cfu/ml was sufficient to distinguish asymptomatic bacteriuria from symptomatic urinary tract infection in 96% of cases. [115] Whether this data is entirely generalisable to the paediatric population is contested in the literature. [22 24]

Other guidelines including the American Academy of Pediatrics (AAP) UTI Guideline propose a lower cutoff of 50,000 colonies per ml, [15 60] which may reflect the higher proportion of samples collected by catheterisation in the US. Specifically lower cutoffs are recommended in many guidelines for samples collected by invasive catheter and suprapubic needle aspiration (SPA)

methods, [12 18 24] as these methods are less likely to be contaminated by incidental skin flora. Many guidelines suggest that any growth from SPA is likely to be significant, regardless of CFU level. [12 19 60] Further detail regarding contamination of specific methods is discussed subsequently in section 2.4.

Even lower CFU cutoffs have been proposed in order to increase the sensitivity of urine culture to detect UTI. A lower cutoff may have less false negatives, but more false positives. A post-hoc analysis of 111 children with 171 episodes of recurrent UTI from the Randomized Intervention for Children with VesicoUreteral Reflux (RIVUR) trial found that decreasing the CFU threshold for clean catch or midstream samples from 100,000 to 50,000 cfu/ml would not have resulted in any further UTI diagnoses. [116] Dropping to 10,000 cfu/ml would have resulted in two further UTI diagnoses. Further prospective research may help clarify the optimal CFU count for diagnosing paediatric UTI.

Mixed growth (contamination) refers to the bacterial growth of more than one species from the laboratory culture. It is assumed clinically that UTI is caused by a single uropathogenic organism, and therefore growth of more than one organism indicates sample contamination with incidental skin flora. Children with anatomical or neurological abnormalities of the urogenital system may however be susceptible to multi-organism infections. [6] Mixed growth may also represent true infection, where the uropathogenic culprit is hidden in a ‘soup’ of skin flora contaminants in the petri dish. Newer genetic evaluations of the urinary microbiome suggests a heterogenous mix of bacteria is normally present in the urine of asymptomatic individuals. [117]

Operational differences exist between laboratories for definitions of UTI and contamination. As described previously, guidelines vary for CFU counts to determine UTI. Further, laboratories have different contamination definitions in the presence of mixed growth for CFU counts, which are required to determine whether one species predominates. These operational differences are not well acknowledged in the literature, but limit comparison of the reported UTI and contamination rates between published studies.

Criteria for what CFU counts are significant in diagnosing childhood UTI are therefore not absolute. [60] Growths at lower CFU may represent early infection, contamination or asymptomatic bacteriuria, and mixed growth may mask true UTI. It is not possible to adhere strictly to culture results and microbiological guideline definitions of UTI in isolation, [6] without considering the result in the context of the clinical findings, dipstick and microscopy results. While a degree of diagnostic ambiguity exists when interpreting urine test results, the waters are far murkier with no urine sample testing at all.

2.3.3 Emerging diagnostic technologies

While current diagnostic confirmation of childhood UTI relies on laboratory culture, limitations of this approach have led to alternate approaches emerging. New genetic technologies have allowed the evaluation of urinary organisms with the sequencing and identification of bacterial deoxyribonucleic acid (DNA) in the urine. Currently this technology is a research tool and not in mainstream clinical practice, but studies have shown that genetic and genomic urine analysis can identify potential uropathogens missed conventionally due to their specific laboratory growth requirements. [118] [119] Metagenomic testing has also shed further light on the normal urinary microbiome, and this heterogenous ‘soup’ of organisms present in asymptomatic individuals. [118]

Polymerase chain reaction (PCR) testing has the potential for use as a rapid diagnostic tool for UTI. It has been evaluated in several adult studies and some paediatric studies, predominantly to identify the presence of E.coli in the urine. [120] Given E.coli is the uropathogen responsible for the majority of childhood UTI, real time PCR has potential clinical utility. However real time PCR was less reliable for the detection of other uropathogens such as Klebsiella species, suggesting further investigation is required before PCR urine testing can be used clinically for UTI diagnosis.

Newer urinary biomarkers have been proposed to differentiate cases of active infection from asymptomatic bacteria. These include cytokines produced in

response to infection in the urinary tract such as interleukins 6 and 8, [121] [122] which have been found in higher concentrations in children with febrile UTI compared to those with asymptomatic bacteriuria. [122] However the clinical utility and cost-effectiveness of these new biomarkers over systemic markers such as C-reactive protein, and their sensitivity and specificity for paediatric UTI, has not yet been sufficiently established to see their introduction into routine clinical practice.

The normal urinary microbiome exhibits significant heterogeneity and diversity. Potentially uropathogenic bacteria may be innocent bystanders in cases of asymptomatic bacteriuria. Therefore the genetic identification of specific bacteria in the urine is unlikely to become a stand-alone diagnostic tool, but could foreseeably be used to supplement existing UTI evaluation methods in the future. Genetic tests for UTI may evolve as the costs of these technologies fall. Novel urinary biomarkers of UTI may likewise have a role in screening and diagnosis in the future. However for now we continue to rely on culture from an appropriately collected urine sample to confirm UTI diagnosis, and these technologies do not change the need to collect a sample for UTI evaluation in the first instance.

2.3.4 Summary of screening and diagnostic tests

The preceding sections have described the sequential screening and diagnostic tests used when childhood UTI must be evaluated (Table 1). Dipstick and microscopy screening can be used to guide initial management, but culture confirmation with evidence of active infection is the gold standard for diagnosis.

The preceding sections have also highlighted some of the limitations and diagnostic pitfalls that are commonly encountered by clinicians. This combination of a clinical conundrum, screening speculation and tangle of tests may leave clinicians feeling that childhood UTI frequently presents as a difficult diagnostic dilemma.

Table 1: Limitations of current methods of evaluating childhood UTI

EVALUATION	LIMITATIONS
Signs and symptoms	Non-specific and variable in childhood UTI History not possible from young pre-verbal children
Dipstick: nitrites	Not produced by all uropathogens (lacks sensitivity) Can be flushed away with frequent voiding
Dipstick: leucocytes	Sterile pyuria with other infections (lacks specificity) Can be absent in early infection
Microscopy: bacteria	Timely results not available in all settings Asymptomatic bacteriuria
Culture	Colony count thresholds to define UTI not absolute Contamination with incidental skin organisms
Emerging genetic tests	May detect normal urinary microbiome organisms At present expensive and not widely available

The challenges are greatest in young pre-continent children. Non-verbal children are less able to indicate localising signs such as dysuria or lower abdominal pain. Clinical signs of UTI overlap significantly with many common viral illnesses of early childhood, such as upper respiratory tract infections and gastroenteritis. Therefore diagnostic confidence requires a combination of appropriate clinical findings, supportive screening tests, with laboratory pyuria and culture confirmation, though the full hand may not be present in all young children with UTI.

Diagnostic imperfections in healthcare are not unique to childhood UTI, though urine sample collection remains a crucial step in the UTI diagnostic pathway. The vital importance of obtaining a urine sample to properly

evaluate childhood UTI cannot be understated. Without a urine sample, no screening or diagnostic tests can be performed at all. Therefore research to understand and improve the urine sample collection process is likely to have an immediate and significant benefit amidst the 'murky waters' of paediatric UTI.

2.4 URINE SAMPLE COLLECTION METHODS

"There are many situations, in primary and secondary care, when a urine sample is required as part of the safe management of an infant or child, yet the practicalities of obtaining samples can be upsetting for children and challenging for both carers and practitioners."

Kilonback (2017) [123]

The preceding discussion of the clinical signs and diagnostic tests for childhood UTI leads into this exploration of the methods used to collect the necessary urine samples for UTI evaluation. The urine sample is mandatory to conduct these tests to diagnose or exclude UTI, but obtaining the sample is often a challenging and frustrating process. [123]

Older toilet-trained (continent) children and adults are able to void on command, enabling relatively straightforward collection of a sample from the urinary stream. Younger pre-continent children are not able to void on command, so reliable samples can be difficult to obtain. [124-126] In younger children samples can be collected opportunistically upon spontaneous voiding using non-invasive collection methods (collected in a urine bag, nappy pad or clean catch of the urinary stream) or extracted directly from the bladder using invasive collection methods (catheter or suprapubic needle aspiration).

Each collection method has advantages and limitations (Figure 4 & Table 2). Waiting for a child to void spontaneously and collecting a sample when they do may take a long time, or be unsuccessful. [127] Taking urine directly from the bladder may be more successful, but is invasive and painful for the child. [128]

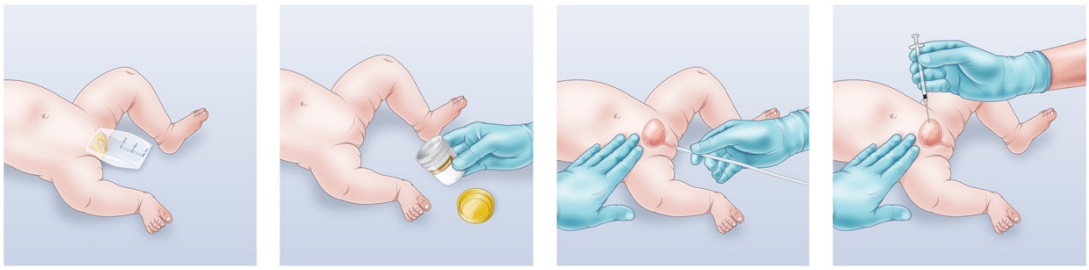
[129] Samples can be contaminated during collection with incidental skin flora, corrupting the test result, [3 24 130] particularly for non-invasive methods. Equipment, resources, expertise or technical skill may be required, especially for invasive methods. The decision on which collection method to use therefore must balance all of these factors, to select the method most suited to the individual patient and clinical context.

Table 2: Advantages and limitations of common collection methods

METHOD	ADVANTAGES	LIMITATIONS
Nappy pad	Convenient Can be used to exclude UTI	Very high contamination: ≤ 60% [42] Unreliable to confirm UTI
Urine bag	Convenient Can be used to exclude UTI	High contamination: ≈ 50% [130 131] Unreliable to confirm UTI
Clean catch	No equipment required More reliable than pad/bag to confirm UTI	Moderate contamination: ≈ 25% [3] Can be time-consuming or unsuccessful
Catheter	Low contamination: ≈ 10% [3] Effective if little urine in bladder Very reliable to confirm UTI	Equipment & expertise required Invasive and painful for the child
SPA	Ultra-low contamination: 1% [3] Can increase success with ultrasound Very reliable to confirm UTI	Equipment & expertise required Invasive and painful for the child

Table adapted from Paper 8: Kaufman et al, BJGP 2020 [132]

Figure 4: Common collection methods for young pre-continent children



urine bag | clean catch | catheter | SPA

Images by the doctoral candidate and Mr Bill Reid, Royal Children's Hospital

The methods used and challenges of urine sample collection in young pre-continent children will now be explored in detail, highlighting the opportunity for research to improve the diagnosis of UTI through practical and effective sample collection in this population.

2.4.1 Continent children and adults

Older toilet-trained (continent) children and adults are usually able to provide a midstream urine (MSU) sample on request. A urine specimen jar is provided, with instructions for the steps required to minimise undesirable sample contamination with incidental skin flora from the genitalia, hands or environment. This includes the collector washing their hands or wearing gloves, avoiding touching the inside of the specimen jar, preventing the specimen jar from touching the perigenital skin or surrounding environment, and placing the lid on the specimen jar as soon as a sample is collected.

Midstream rather than first void collection is recommended, to reduce sample contamination with incidental periurethral skin organisms. The first part of the void goes into the toilet, hopefully carrying any potentially contaminating organisms along with it. A sample is then collected from the middle of the stream, reducing the likelihood of acquiring contaminating incidental organisms.

This thesis focuses on methods of sample collection for younger pre-continent children who are unable to provide a voluntary midstream urine sample.

2.4.2 Pre-continent children: non-invasive collection methods

Younger children who are not yet toilet-trained (pre-continent) are not able to void on demand for urine sample collection. Non-invasive collection methods for pre-continent children rely on waiting for the child to void spontaneously, and opportunistically collecting a sample when they do.

2.4.2.1 Urine bags

Urine collection bags are a popular method of urine sample collection, [133] particularly in primary care and outside of the hospital setting. [126 134] The adhesive bag is attached over the child's genitalia and collects a urine sample when the child voids. They are commonly placed inside the nappy, or a slit can be made in the nappy so the bag can be visualised. [135] While seemingly convenient, the bags can detach or leak, so vigilance is still required. Discomfort and skin irritation with removal of the bag may be reported by parents. [136] Average collection time for bag specimens was 85 minutes in one small observational study of 23 children. [131] Success of bag urine collection attempts is reported as 82-96%. [131 136 137]

Contamination, which corrupts the test result, is the major limitation of bag urine collection. This is understandable given the bag is in continuous contact with the perigenital skin, which is known to be colonised with faecal flora. A meta-analysis of 21 studies including 7659 samples showed a contamination rate of 46%, with a false-positive rate of 61%, for urine collection bag samples. [130] A local observational study in a paediatric ED setting found a similar contamination rate. [3] Skin cleaning with antiseptic chlorhexidine solution prior to bag urine collection is not effective in reducing contamination rates. [138] So while urine collection bags are favoured in some settings as an easy way to collect a urine sample, unacceptably high contamination rates may limit their diagnostic utility.

2.4.2.2 Nappy pads

Nappy pads are used in some settings for non-invasive urine collection from young children, and are mentioned as an acceptable alternative to clean catch collection in UK guidelines. [65] The absorbent pad is placed inside the nappy, and urine extracted with a syringe after the child voids. Nappy pads are most commonly used in the primary care setting, [139] but are not used in all countries.

Like urine bags, the pad is in continuous contact with the perigenital skin, and faecal soiling can occur with defecation. The contamination rate of nappy pad samples has been shown to be as high as 62%,[42] and 5-7 times greater than the contamination of clean catch samples in studies where both collection methods are utilised. [42] [139] Like urine bags, this high contamination rate limits diagnostic utility.

2.4.2.3 Clean catch

The clean catch urine (CCU) collection method replicates the midstream technique used in older children and adults, but relies on substantial patience, vigilance and quick reflexes for successful execution. The nappy is removed, and the perigenital skin is cleaned to reduce the risk of sample contamination. A clinician, parent or carer waits with a specimen jar ready, to opportunistically catch a sample when the child voids. Ideally a midstream sample is collected, although in practice this may be difficult to achieve. This may be even more challenging in female patients, where the urinary stream may be less forceful than in male patients where the longer urethra creates a hose-like effect.

Importantly, clean catch has significantly lower contamination than bag urine collection, reported between 5-27%. [137] [140] [141] Local studies in the ED setting show a contamination rate of 26%. [3]

Clean catch is often the preferred non-invasive collection method, [142] but attempts can be time-consuming or unsuccessful. Collection attempts may be abandoned by parents or clinicians, and some parents report clean catch is

messy. [136] One previous study in the ED setting found that 58% of CCU attempts lasted longer than one hour, with a mean time spent attempting collection of 71 minutes. [127] Success of CCU attempts is reported as 79-85%, [127 137] and point of care ultrasound evaluation of bladder volume has not been shown to increase the success of CCU attempts. [143]

Relative to how commonly it is used in clinical practice, there is a paucity of data for outcomes of CCU collection attempts, particularly for children with possible UTI who can be dehydrated and unwell, which may affect voiding frequency. A co-authored observational study of clean catch outcomes, conducted to address this knowledge gap and inform the clinical studies in this thesis, is reported subsequently in Chapter 4 .

2.4.2.4 Other non-invasive methods

Cotton wool balls, a midstream urine collection device and washed potties have all been proposed as alternative non-invasive collection methods. Cotton wool balls are placed inside the nappy to absorb urine, similar to nappy pads. However they are highly prone to contamination, and UK guidelines specifically recommend against their use. [65] A midstream urine collection device has been proposed to reduce contamination of spontaneously voided samples, which directs and separates urine flow to discard the first void and collect a midstream sample. However the device did not improve contamination beyond standard urine collection bags. [144] Collection of spontaneously voided urine into sterilised or washed potties, similar to an adult voiding into a bed pan, also lacks evidence for reduced contamination compared to bag specimens. [145 146]

2.4.2.5 Main limitations of non-invasive collection

As described above, while non-invasive collection methods seem convenient, their clinical utility is limited by the:

- time taken for collection attempts
- likelihood of collection success
- likelihood of sample contamination

Waiting for spontaneous voiding in young children can take a long time. In particular, children who require evaluation for UTI are often unwell and dehydrated due to vomiting or poor feeding, with corresponding low urine output. The bladder may also be empty due to recent voiding. Non-invasive collection methods therefore can be time-consuming, and not always successful.

Sample contamination corrupts the culture result, making it impossible to definitively diagnose or exclude UTI. Nappy pads and urine bags have contamination and false-positive rates reported as high as 50-60%, [42 130] meaning a negative result helps to exclude UTI but their diagnostic utility to confirm UTI is limited.

Consequently, while improved non-invasive collection would be of major benefit, invasive collection methods are used in some settings to overcome the unreliability of non-invasive collection.

2.4.3 Pre-continent children: invasive collection methods

Invasive urine collection methods use a catheter or needle to extract urine directly from the bladder. Invasive methods may be used where initial non-invasive methods are unsuccessful, or if non-invasive collection is undesirable due to time or potential contamination.

Full detail for how to perform catheterisation and suprapubic needle aspiration procedures is included in a clinical review article published by the doctoral candidate (Paper 7), which is included in Appendix 11.1.2.

2.4.3.1 Catheterisation

Urethral catheterisation involves inserting a catheter tube through the urethra and into the bladder. The tube is removed once a urine sample is obtained, and is sometimes referred to as an “in-out catheter” procedure. Catheterisation is performed by a nurse or doctor, and requires a degree of specialised training and experience. Such expertise may not be universal

outside of the paediatric specialist setting. Specific equipment is also required, including an appropriately sized sterile urinary catheter or feeding tube. The success rate of catheter urine collection may vary with the level of experience of the operator, and has been reported as 68-100%. [128 129 147-151]

As an invasive procedure, significant pain and distress may be caused to the child, despite the use of analgesic agents. [4 128 147 152] Contamination for catheter urine samples is reported at 5-19%, [129 152-154] and 12% in a local study in the ED setting, [3] which is significantly lower than non-invasive methods. A further advantage of the catheter method is higher collection success when there is less urine present in the bladder.

2.4.3.2 Suprapubic needle aspiration

Suprapubic needle aspiration (SPA) is regarded as the gold standard for uncontaminated sample collection in Australian guidelines. [16] SPA involves inserting a needle through the skin of the lower abdomen, into the bladder, and aspirating a sample of urine. SPA has the lowest contamination of all collection methods, reported as 0-1%. [3 4 129 154] Success for SPA procedures is reported as 31-80%, [129 148 155-159] which is lower than for catheterisation. Success may also vary with the experience of the operator and clinical condition of the child, and some equipment is required including a topical anaesthetic agent and appropriately sized needle and syringe. SPA causes a similar or greater level of pain and discomfort to catheterisation, [129] though the duration of the procedure may be shorter. [4]

Adequate bladder urinary volume may determine the success of urine collection procedures, particularly SPA. Ultrasound evaluation of bladder urine volume can therefore optimise the timing and success of procedure attempts. If the bladder is relatively empty, clinicians may choose to optimise hydration to increase urine output and bladder volume. Several studies have shown that bedside ultrasound evaluation can increase the success of catheter and SPA procedures. [149-151 155-158 160 161] While ultrasound is non-invasive and also does not impart radiation, the equipment and expertise required may limit its widespread use. Volumetric bladder scanners have been shown to be

inaccurate, [162] and portable ultrasound is not widely available outside of specialist settings.

2.4.3.3 Complications associated with invasive specimen collection

Complications and adverse events can occur as a result of invasive urine collection procedures. As well as pain and distress, and procedure failure, adverse events be caused during and after invasive urine sample collection from both urethral instrumentation with catheterisation, and anterior abdominal wall penetration with SPA.

A common short-term complication of catheterisation is haematuria, which is usually transient and self-resolving in the absence of unexpected procedural trauma. Serious immediate complications have not been reported in the literature from diagnostic catheterisation to evaluate potential childhood UTI. Serious immediate complications from catheterisation have been reported in other specific contexts such as neonatal or adult populations, or with intermittent catheterisation or urological procedures. These serious complications include catheter induced bladder rupture and urethral injury. [163] [164] The risk of serious short-term adverse events with catheterisation in these other specific populations is estimated at 1%. [149]

Complications may also occur in the medium term after catheterisation. In a prospective study of 200 children aged 3-24 months who underwent diagnostic catheterisation in the ED, 21% of patients suffered a complication in the week following the procedure. [165] These included dysuria (10%), urinary retention (6%), haematuria (5%) and secondary UTI (0.5%), although few required further medical attention (1%). Another study of 124 children reported a lower complication rate of 4% in the month following catheterisation in the ED, including dysuria (2%), haematuria (1%) and secondary UTI (1%). [166]

There is plausible concern for long-term complications following invasive urine collection procedures, particularly instrumentation causing urethral trauma with catheterisation. Some authors have recommended caution with

catheterisation due to the risk of longer term development of urethral stricture, although this risk has not been quantified. [148]

The most common short-term complication of SPA is also haematuria, which is usually transient and self-resolving in the absence of unexpected procedural trauma. Abdominal wall and intramural bladder haematomas may also occur, [167] [168] but can be managed conservatively.

Serious complications are rare but have been reported with SPA procedures. Penetration of the bowel can occur during the attempted bladder aspiration. Aspiration of faecal matter would alert the operator to this complication, although it may also be unrecognised during the procedure. More significant complications due to trauma to non-bladder structures, including suprapubic abscess, massive haemoperitoneum and anaerobic bacteraemia, have also been reported in the literature. [169-171]

Invasive procedures are by their very nature aggressive and intrusive. Though the rate of significant adverse events is low, catheterisation and SPA have the potential to cause immediate and serious complications for a small minority of patients.

2.4.3.4 Main limitations of invasive methods

As described above, invasive collection methods have lower contamination rates than non-invasive methods, and can be more effective, however invasive methods:

- cause significant pain and distress to the child
- can cause complications, though most are minor and transient
- require equipment and expertise that may not be universally available

Therefore while catheterisation and SPA may be indicated in some circumstances, these procedures are not always possible or practical, particularly in primary care and resource-limited settings.

2.4.4 Sample contamination during voiding and collection

Contamination of urine samples is a common barrier to accurate UTI evaluation. Contamination occurs when incidental skin flora organisms enter the sample, which may obscure true uropathogenic organisms, or masquerade as them. This corrupts the culture test result and can cloud UTI diagnosis or exclusion, or lead to false-positive results. Sample contamination may necessitate repeat sample collection.

Unfortunately the nature of the collection process and patient factors in the young patient population means avoiding sample contamination is not easy. Young children, particularly those who are unwell and distressed, are unlikely to lie still for the collection procedure. Parents are often the assistants or catchers for the urine collection attempts, but may be fatigued or distracted if their child has been unwell. Clinicians may hurry collection procedures to minimise discomfort for the child.

Skin is normally colonised with various incidental commensal bacteria. These potentially corrupting skin flora organisms can originate from either the collector or the patient. The skin of the collector's hands are colonised with incidental bacteria, [172] which can enter the urine sample if they inadvertently touch the inside of the collection jar. The patient's skin is also colonised with bacteria, which can potentially contaminate and corrupt the sample. Previous studies have shown perimeatal colonisation on swab culture in up to 97% of children less than two years of age, [138] with E.coli vaginal colonisation in 90% of girls in this age group. [173] These organisms can enter the urine if the specimen jar is held directly against the perigenital skin of the child.

Contamination with skin flora organisms can also occur when urine flushes the perigenital skin upon voiding. This phenomenon can be observed in fluoroscopic studies, which demonstrate urine flushing the vagina or foreskin on voiding. During spontaneous voiding in paediatric micturating cystourethrogram studies, ballooning of the foreskin has been demonstrated in 38% of boys, and flushing of the vagina in 14% of girls. [26]

The urethra is also colonised with bacteria. Urine voided from the bladder is expelled via the urethra, which may transfer these bacteria into the sample, particularly in the first voided urine. The contamination of early stream samples has been shown to be three times greater than from midstream samples from young uncircumcised boys under general anaesthesia. [174] For this reason it is often suggested to discard the first part of the urine stream, to allow any urethral flora to be washed away, and then to collect a midstream sample. While collection of a midstream sample may be possible in continent and co-operative patients, or with catheterisation, with clean catch attempts in a young pre-continent child this may be practically challenging.

As described previously, contamination rates vary between collection methods, but are generally higher for non-invasive methods. Comparing reported contamination rates between studies and centres, however, may be limited by variable laboratory and research definitions of contamination. For example, reported sample contamination rates in 2 similar studies conducted in similar primary care settings ranged from 12-62% for nappy pad samples, and 2-13% for clean catch samples. [42] [139] Further complicating contamination comparison, some studies consider clean catch to be limited to opportunistic sample collection from pre-continent children, while other studies also refer to midstream samples from continent children as clean catches. Studies reporting contamination of multiple collection methods from the same centre generally show the same contamination hierarchy from nappy pads and urine bags (highest), descending through clean catch, catherisation, to SPA (lowest). [3] [137] [139]

2.4.4.1 Skin cleaning to reduce contamination

Perigenital skin cleaning prior to urine sample collection is generally recommended, [175] to reduce the burden of skin flora organisms which could inadvertently enter the urine sample. Different cleaning methods have been proposed and evaluated. Cleaning with water or saline has a mechanical rinsing effect, which may remove debris and some skin flora organisms. Cleaning with soap has a mechanical washing effect, akin to the process of removing organisms with handwashing using soap. Cleansing with

antibacterial agents such as chlorhexidine or iodine has a bactericidal effect, killing bacteria via disruption of the cell membrane.

For adult populations, all of these cleaning methods have been demonstrated in studies to reduce midstream sample contamination, with antibacterial cleansing having the greatest effect. [176-178] However not all studies have shown significant reductions in contamination, so further trials or meta-analysis of results may be required. [177] [179-181]

For continent children there are limited studies of skin cleaning to reduce sample contamination. One randomised trial demonstrated that soap cleaning reduced the contamination of midstream samples from 24% to 8% for toilet-trained children in a Canadian ED. [182] Other non-randomised studies have not shown benefit from soap cleansing. [183] [184] Another non-randomised study showed that saline cleaning reduced contamination for predominantly older toilet-trained Danish children. [185]

For younger pre-continent children there are no studies to suggest the optimal method of pre-collection perigenital skin cleaning before non-invasive collection. One Canadian study showed that although chlorhexidine cleaning reduced perimeatal flora for 25% of infants, it did not reduce bag sample contamination. [138] While most international UTI guidelines do recommend cleaning before sample collection, none except for the Australian guideline specifies the actual method of cleaning, which recommends cleaning with saline-soaked gauze before clean catch collection. [16]

Sample contamination is a major limitation for the otherwise convenient and practical non-invasive urine sample collection methods used for young pre-continent children. Further research is required to define optimal pre-collection cleaning practices in this population. While beyond the scope of this thesis, the doctoral candidate's planned post-doctoral research studies which will tackle this issue are outlined further in section 9.7.

2.4.5 Guideline recommendations

Effectively evaluating suspected UTI and unexplained fever in young children, while balancing under and over investigation, is a constant challenge for clinicians. Clinical practice guidelines are a resource to guide evaluation and care for specific conditions. Ideally they are informed by relevant evidence, though they may also incorporate consensus and expert opinion, to produce advice tailored for the specific audience and environment. Therefore there may be geographical variation in guideline recommendations according to the clinical context for which they are written. International guideline recommendations for urine sample collection from young pre-continent children are summarised below in Table 3, although individual hospitals often have their own guidelines.

Table 3: Guideline recommendations for collection methods

GUIDELINE	RECOMMENDATIONS
UK and European guidelines	
National Institute for Health and Care Excellence UK [186]	- **Clean catch** recommended method - If catch unobtainable, use other non-invasive method - Do not use cotton wool balls, gauze or sanitary towels - Catheter or SPA if non-invasive methods not possible/practical
European Association of Urology / Paediatric Urology [12]	- **Clean catch, catheter and SPA** recommended methods - SPA method of choice due to least contamination - Bag specimens can be used for screening
Italian Society for Paediatric Nephrology [104]	- **Clean catch** recommended method in primary care - **Catheter** recommended in hospital settings - Bag specimens not recommended
French Pediatrics Society [187]	- **Clean catch, catheter and SPA** recommended methods - Bag specimens cannot be used to confirm UTI
Dutch Association for Pediatrics [188]	- **Clean catch or catheter** recommended methods - Bag specimens can be used for screening

Spanish Association of Paediatrics [189]	- **Catheter or SPA** recommended methods - Bag and clean catch useful for screening - Bag specimens should not be sent for culture
North American guidelines	
American Academy of Pediatrics [23]	- **Catheter or SPA** sample required to diagnose UTI - Can use convenient sampling to obtain urine for screening - Must confirm positive screening with catheter or SPA
Canadian Pediatric Society [60]	- **Catheter or SPA** recommended methods - Bag specimens should not be sent for culture
Australian guidelines	
Victorian Statewide Clinical Practice Guidelines [16]	- **Clean catch** appropriate if child not severely unwell - SPA is gold standard - Bag specimen not recommended for culture
Kidney Health Australia Caring for Australians with Renal Impairment [19]	**- Clean catch, catheter or SPA** recommended methods - SPA is gold standard - Positive bag culture should be confirmed by other method
Other national guidelines	
Israeli Medical Association [190]	- **Catheter or SPA** recommended for pre-continent children - Clean catch acceptable for circumcised males - Bag specimen not recommended for culture
Indian Society of Paediatric Nephrology [191]	- **Clean catch** recommended method - Catheter or SPA recommended for neonates and infants
Guidelines for resource limited settings	
World Health Organisation [21]	- **Clean catch** recommended method - SPA recommended for sick infants

International guideline recommendations for urine sample collection for UTI in young pre-continent children. Table adapted from Paper 7: Kaufman J, ADC Education & Practice 2019 [192]

Why do these guidelines have inconsistent and sometimes conflicting recommendations for the same clinical condition? In part these differences

may be explained by geographical variation in service provision and resource availability, which influences what is possible and practical in that setting.

2.4.5.1 Guidelines favouring non-invasive collection methods

Some guidelines recommend non-invasive collection methods as first line, including the Australian and UK guidelines. [16] [186] In the healthcare systems of these countries, most unwell children with fever will present to general practice or a general hospital ED. Therefore in these countries most children will be seen by a non-paediatric healthcare professional.

The National Institute for Health and Care Excellence (NICE) UK Clinical Guideline for Urinary Tract Infection in Under 16s: Diagnosis and Management is a major international paediatric UTI guideline. It states that "the aim of urine collection is to obtain a good-quality sample from which the diagnosis of UTI can be confidently confirmed or excluded." [6] The NICE guideline also assumes a primary healthcare perspective where children present initially to their general practice doctor, and that "since the majority of children presenting with a UTI in the UK are likely to present in primary care, the collection of a urine specimen needs to be simple, reliable, cost effective and acceptable to children, parents and carers." [6] Accordingly, non-invasive collection methods are recommended, [186] with clean catch recommended over bag and pad collection due to lower contamination rates. Invasive collection methods are acknowledged as the "reference standard" but described as "not suitable as a method of urine collection in primary care". [6] It is suggested invasive collection may be appropriate in the hospital setting when the child is more unwell or requires more urgent antibiotic therapy.

2.4.5.2 Guidelines favouring invasive collection methods

In contrast, other guidelines recommend invasive collection methods as first line, including American and many European guidelines. In the US and some parts of Europe, children may present directly to a paediatrician for medical care, and therefore are more likely to be evaluated by a specialist paediatric healthcare professional.

The American Academy of Pediatrics (AAP) 2011 Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months is another major international guideline for paediatric UTI. [15] The AAP Guideline assumes a US healthcare perspective, where children more frequently present directly to a paediatrician or ED than in the general practice focused UK healthcare system. Invasive collection methods are more practical in this specialist setting, where the requisite skills and equipment are more likely available. The AAP Guideline accordingly favours invasive collection, and suggests for unwell infants that "if the clinician determines that the degree of illness warrants immediate antimicrobial therapy, then a urine specimen suitable for culture should be obtained through catheterisation or SPA before antimicrobial agents are administered". [15] With regard to non-invasive collection the guideline states that "cultures of urine specimens collected in a bag applied to the perineum have an unacceptably high false-positive rate and are valid only when they yield negative results." [15] As such, non-invasive collection is only recommended to rule out infection, with confirmation by a more reliable method required if this is suggestive of infection. The AAP Guideline states that for less unwell infants still considered at risk of UTI that "if the clinician determines that the febrile infant is not in a low-risk group, then there are 2 choices. Option 1 is to obtain a urine specimen through catheterisation or SPA for culture and urinalysis. Option 2 is to obtain a urine specimen through the most convenient means and to perform a urinalysis. If the urinalysis results suggest a UTI, then a urine specimen should be obtained through catheterisation or SPA and cultured." [15] Interestingly the previous 2011 AAP Guideline does not even mention the use of clean catch as a non-invasive collection method, despite its widespread use in other settings. The 2016 reaffirmation of the AAP Guideline continues the same recommendations, but does mention the clean catch collection method as a non-invasive option stating that "urine collected in a bag or via a clean catch method is suitable for urinalysis, but such specimens (especially urine collected in a bag) are less appropriate for culture." [23]

Of note, while it recommends the use of invasive collection methods, the AAP Guideline specifically identifies as an area for further research that "the

development of techniques that would permit an alternative to invasive sampling and culture would be valuable for general use". [15]

2.4.5.3 Guidelines for resource limited settings

The World Health Organisation (WHO) Pocketbook of Hospital Care is designed for use by healthcare workers at a primary care level in developing world countries. It provides guidelines suitable for the care of children as inpatients and outpatients in small hospitals and larger health centres where basic laboratory facilities and inexpensive medicines are available. [21]

The WHO Pocketbook recommendation for investigation of UTI is "If possible, obtain a clean catch urine sample for culture. In sick infants, supra-pubic aspiration may be required". [21]

2.4.5.4 Compliance with guideline recommendations

Several studies have shown that in practice the compliance with guideline recommendations, for the method of urine sample collection and other related aspects of care, is variable.

A 2010 UK study retrospectively audited the implementation of NICE guidance on urinary tract infections in children in primary and secondary care. [193] For 1149 children from 10 general practices, 3 paediatric units, 2 paediatric emergency units and 2 emergency general units, the study found guideline compliance varied from 13-89% across 5 criteria. For Criterion 1, that "all children under 3 years of age presenting with unexplained fever ≥38°C should have a urine sample tested within 24 hours, compliance was 28%. [193]

A 2004 US retrospective cohort study found overall that less than 50% of paediatric UTI cases under 1 year of age received the recommended medical care. [194] A 2008 US study based on retrospective chart review found that at the authors teaching institution there was 70% adherence to recommendations for method of urine collection. [195] A 2014 survey of 155 US paediatricians found up to 18% non-compliance with recommendations for method of urine collection. [125]

2.4.5.5 Summary of guideline recommendations

In summary, guidelines have conflicting recommendations regarding the method of urine sample collection for young pre-continent children, reflecting the different perspectives from which they are written. What may be an appropriate recommendation for a child presenting to a hospital specialist may differ from what is appropriate for a child presenting to primary care in the community.

Compliance with guideline recommendations is not complete. Collection by the recommended method may not always be possible or actually take place. Ultimately all guidelines recommend that a urine sample is required to diagnose UTI, though with varied recommendations for the method of collection.

2.4.6 Clinician and parental preferences

While guidelines have differing recommendations for the optimal method of urine sample collection, research has demonstrated that clinicians as well as parents also have different preferences.

2.4.6.1 UK clinicians

In 1997 Vernon et al surveyed 333 English general practitioners (GPs), and found approximately 40% of samples from pre-continent children were collected using urine pads or bags, 17% clean catch, 11% sent to hospital or another person given responsibility for collection, 1% cotton wool balls inside the nappy, and the remainder uncertain or missing responses. [146]

In 2008, Kennedy et al surveyed 50 Irish GPs regarding their current practice managing paediatric UTI. [126] If advising parents regarding collecting a urine sample from a one year old child, 80% would use a urine bag and 20% clean catch.

The Diagnosis and Treatment of Urinary Tract Infection in Young Children in Primary Care (DUTY) Study was a large prospective cohort study of 7163 children under 5 years of age from 50 primary care sites across England and Wales. [43] The study protocol was to use urine nappy pads for sample collection in nappy wearing children and "those in whom the parent/guardian did not think clean-catch would be successful". [139] Urine samples were collected with urine pads in 3205 cases and by clean catch in 3036 cases. [139] The study authors reported that the urine pads were used for the majority of children less than 2 years of age, whereas for older children with a mean age of 3.5 years the clean catch method was predominantly used, although this definition of clean catch would also encompass continent children providing a midstream urine.

2.4.6.2 European clinicians

In 2014 Hadjipanayis et al surveyed 1129 paediatricians from primary and secondary care practices in Europe. [134] They found that the preferred methods of collection for infants less than 3 months of age was urine bag (53%), clean catch (20%), catheter (20%), SPA (4%) and other (3%). For children 4-36 months of age preferences were urine bag (59%), clean catch (28%), catheter (11%) and other (3%). [134] Interestingly there was noticeable heterogeneity in responses between countries, for example in Germany urine bags were the overwhelmingly favoured method while in Poland urine bags were unpopular, and in Italy the clean catch method was more favoured. [134]

2.4.6.3 American clinicians

In a 2002 prospective cohort study by Newman et al of 3066 febrile infants less than 3 months of age seen by a paediatrician in the outpatient setting, the majority of urine samples were obtained by catheterisation (70%), with urine bag (25%), SPA (3%) and clean catch (2%) used less frequently. [196]

In the early 2000s, Schroeder et al conducted a similar follow-up study regarding the choice of urine collection methods by paediatricians. [197] Like in the previous study, the majority (70%) of samples were collected by

catheterisation, with the remainder collected by urine bag (25%), SPA (4%) and clean catch (1%).

In 2008 Shah et al performed a retrospective analysis of both inpatient and outpatient UTI episodes at a teaching hospital based on chart review of 104 patients, of which 49 were aged less than 2 years and 21 were aged 2-4 years. [195] The authors state “the majority of urine samples - 73 (70.2%) - were obtained by catheterisation and the remainder by clean catch”, [195] but it is unclear if “clean catch” also included some older continent children providing a midstream urine sample.

In 2014 Coutinho et al surveyed 155 paediatricians, finding 46% preferred catherisation, 35% would consider the clinical scenario, 8% would start with a bag specimen then use catheterisation/SPA as required, and 3% other methods such as SPA and clean catch. [125]

In 2016 Selekman et al surveyed 366 physicians caring for children (87% paediatricians, 5% ED physicians, 2% urologists, 6% other including family medicine) from a random national sample of the American Medical Association Masterfile. [198] Catheterisation was the preferred collection method (74%), with urine bag (25%) and SPA (1%) also used. Urine bags were most commonly used when there was parental refusal (49%) or difficulty (42%) with catheterisation. [198]

2.4.6.4 Australian clinicians

In 2012 Buntsma et al surveyed 109 emergency physicians from paediatric EDs in Australia and New Zealand. [142] The survey stratified responses by 6 categories of patient age and severity of illness. They found for children less than 6 months of age that the preferred collection method was SPA if unwell, and clean catch if not unwell. For older children 7-24 months of age the preferred collection method was catheterisation if unwell, and clean catch if not unwell. [142]

2.4.6.5 Summary of clinician preferences

Overall there is significant heterogeneity in clinician preferences for the optimal method of urine sample collection, both within and between geographical regions and practice groups. In some instances, these studies also reported that clinician preferences were influenced by the preferences of the child's parents.

2.4.6.6 Parental preferences

Parental perceptions and preferences for the care of their child are important. It is therefore logical that parental considerations would influence clinicians' decisions regarding the method of urine sample collection. A recent systematic review found that for paediatric UTI "from the limited literature, it appears that parents would like information about prevention, diagnosis, treatment, and prognosis". [199] However there are few studies investigating parental perception of urine sample collection methods, and how these may influence clinician practice.

In 2000 Liaw et al recruited 44 parents of English children aged less than 18 months, to attempt urine sample collection at home by urine bag, pad and clean catch on consecutive days. [136] Parents reported a preference for using pads then urine bags over clean catch, and that urine bag and pad collection was easier than clean catch collection. Urine bags were reported to be uncomfortable or distressing for the child by most parents. Clean catch was reported to be both time-consuming and messy. [136]

In 2003 Owen et al gathered data from semi-structured questionnaires from 52 parents of Welsh children less than 2 years of age with UTI. [200] 54% responded it was difficult to collect a sample, with most preferring the clean catch method (40%) over pads (37%) and urine bags (23%). The qualitative synthesis highlighted difficulties with urine bag collection, stating "some felt that the bag collection produced unnecessary discomfort for their child whilst others felt that it was difficult to keep the bag in place."

Invasive collection procedures may be perceived negatively by parents due to the pain and distress inflicted on the child. A 2017 cross sectional survey by Selekman et al of 2726 US parents conducted via social media found that 56% perceived extreme distress with catheterisation of their child, and concluded this would likely influence the use of this method in investigating paediatric UTI. [201] In one US study, 49% of clinicians reported that parental refusal of catheterisation would influence their decision to use urine bags as the method of collection. [198] However in another US study, 84% of clinicians reported that parental influence only mildly affected their choice of urine sampling method. [125]

There is conflicting evidence about whether catheterisation or SPA is more painful for infants, which may influence parental perceptions of the procedures. One study found that SPA was more painful for infants less than 2 months of age using parental and nurse assessment of pain, and using a standardised neonatal pain scale. [129] Other studies have shown the pain experienced by infants is similar between catheterisation and SPA procedures. [4]

2.4.7 Treating UTI without a urine sample

Guidelines are clear that a urine sample and culture is required to diagnose UTI, but in practice this may be challenging to actually obtain. Consequentially, empiric antibiotic prescription may occur in some cases where UTI is suspected but not confirmed.

In the US outpatient setting, a retrospective study of an insurance claims database analysed over 40000 episodes of paediatric UTI between 2002-2007, investigating the use of urine testing and urine cultures for antibiotic treated UTI episodes by paediatricians, family physicians, emergency physicians and urologists. [124] Concerningly, in 32% of the 5890 antibiotic treated UTI episodes in children under 2 years, no urinalysis or urine culture was performed at all. [124]

In the 2016 survey by Selekman et al described previously, 84% of doctors reported always collecting a urine sample before initiating treatment for UTI. [198] Respondents reported that they would be more likely to collect urine samples if they were easier to collect (46%) or if results were available immediately at the point of care (48%). [198]

Difficulties with urine sample collection in young pre-continent children therefore translates to suboptimal clinical care where sample collection is not completed. Without culture confirmation, empiric UTI treatment is untargeted or may be unnecessary, contributing to antimicrobial resistance and potentially delaying identification and treatment of the actual problem. Though current collection methods all have limitations, improved collection methods that are acceptable to parents and practical for clinicians could likely improve collection rates.

2.4.8 Summary: variation in practice and preferences

Accurate diagnosis of UTI requires the collection of an uncontaminated urine sample prior to the commencement of antibiotic therapy. [23]

Collecting a reliable urine sample from a young pre-continent child is not straight forward. Existing collection methods all have limitations. There is significant variation in guideline recommendations and clinician preferences for the optimal collection method. Invasive collection methods require equipment and expertise to perform, limiting their use in many settings. Non-invasive collection methods can be time-consuming, unsuccessful and have higher contamination rates. Clean catch is the preferred non-invasive collection method in many guidelines due to its lower contamination rate compared to urine pads and bags. Empiric treatment of UTI without culture confirmation is not uncommon, but is suboptimal.

Improving the effectiveness and acceptability of urine sample collection would have many benefits for patients, clinicians and health services. Developing an improved non-invasive urine sample collection method is highlighted in the

literature as a research priority, [15] and this is the first main research aim reported in this thesis, described further in Chapters 4 and 5.

2.5 COSTS OF URINE SAMPLE COLLECTION

"Appropriate diagnosis and treatment of UTI in children presenting to primary care are particularly challenging because symptoms and signs are often nonspecific. The costs of a urine sample, laboratory test, and antibiotic are relatively low.

The economic impact may, however, be substantial because of the large number of acutely unwell children who present to primary care, additional diagnostic tests for structural abnormalities of the urinary tract, rare but serious complications of UTI, and the wider impact of antibiotic prescribing on bacterial resistance."

Hollingworth et al (2017) [31]

This background section now moves to consider the healthcare system costs of childhood UTI in general, leading to the focus on cost-effective urine sample collection as the second main research aim reported in this thesis.

2.5.1 Costs gradient of childhood UTI

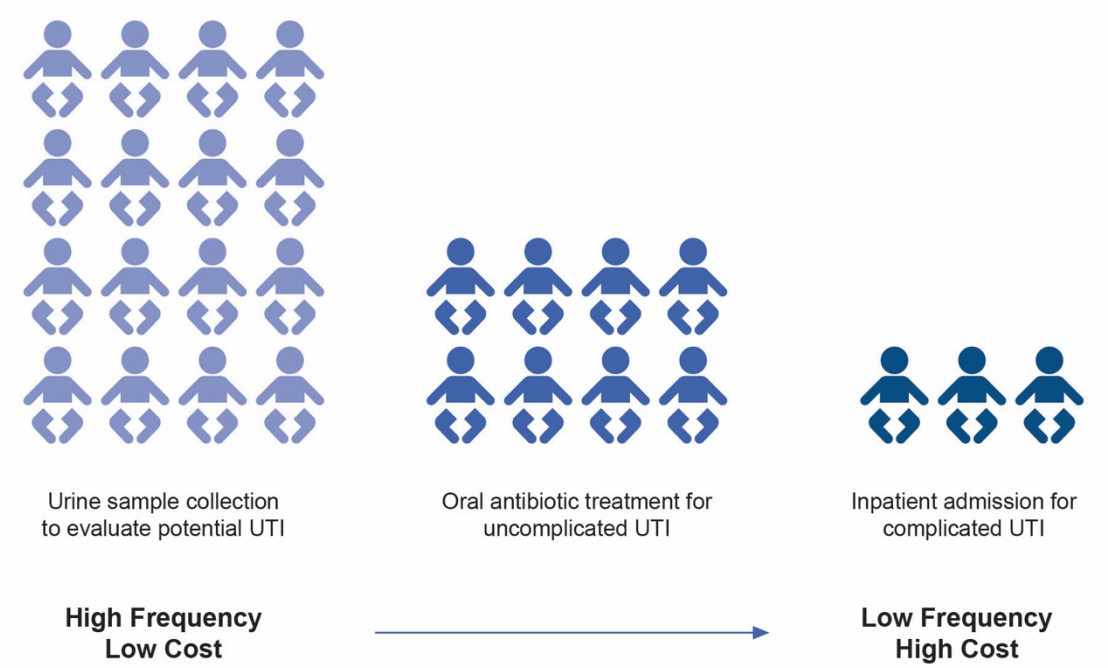
If UTI is suspected clinically, a urine sample must be collected to confirm or exclude the diagnosis. Many young children with unexplained fever also require a urine sample to evaluate potential UTI. Therefore urine sample collection is required for many children, and collecting a sample generates small costs per patient.

Most children diagnosed with UTI can be treated as outpatients with oral antibiotics and managed at home with supportive care. Some of these children may require follow-up and ultrasound imaging of the renal tract,

depending on age, setting and local guideline recommendations. The majority of these children with UTI generate moderate costs per patient.

A smaller proportion of children diagnosed with UTI will require hospital admission, further imaging investigations, and more substantial follow-up. This includes younger, sicker and more complicated cases. Though there are less of these children with complicated UTI, they generate much higher costs per patient.

Figure 5: Costs gradient for paediatric UTI



As such total healthcare costs for childhood UTI accumulate along a gradient (Figure 5), from high frequency with low costs through to low frequency with high costs. Total costs are therefore likely to be substantial at a health system level, although may vary between settings with differing local costs and management practices.

Getting the initial diagnosis right is important for all of these children, to enable timely and targeted treatment of true UTIs, and avoid a cascade of unnecessary management caused by misdiagnosis. Accurate diagnosis relies on collecting an uncontaminated urine sample, and avoiding false positive

results. Optimising the initial evaluation of UTI with effective and cost-effective sample collection could therefore generate substantial healthcare cost savings across this spectrum of patients.

2.5.2 Healthcare system costs of managing childhood UTI

This section now briefly reviews what is known and reported in the literature about the total healthcare system costs of managing childhood UTI. Though childhood UTI is common, there is surprisingly little published data regarding costs.

Costs in this section are reported in the local currency and as unadjusted figures from the time of publication in the original journal articles.

Of note, previous studies and economic evaluations have considered healthcare system costs, but have not included additional parent and carer costs or quality of life measures for children.

2.5.2.1 Health care utilisation and costs of childhood UTI in the US

Childhood UTI is common in the US outpatient and ED context, accounting for 0.5-0.7% of outpatient doctor visits and 5-14% of ED visits by children annually. [1 202] Mean outpatient treatment costs for a single episode for infants with UTI were $239 per male and $267 per female patient in a 1997 US cohort study, [203] though this data is now two decades old. The majority of children with UTI are managed as outpatients, but approximately 5% will require hospital admission. [204]

Childhood UTI is therefore also common in the US hospital inpatient context. It is the tenth most common paediatric hospital admission diagnosis in the US, [205] accounting for 2% of all paediatric hospital admissions. [205] Hospitalization is also more common in younger children. [202 205] In 2006, average hospital costs for paediatric UTI admissions in the US were $3,838, [205] and aggregate hospital charges were reported as >$500 million per year. [205] Studies from that decade also showed that costs were rising. [202 205]

However the US has a largely privatised medical system, US guidelines have different imaging recommendations after first UTI, recommendations have changed over time, and the US spends more money per person and as a percentage of gross domestic product on healthcare than any other country in the world. [205] Costs data from the current decade is lacking. Therefore these US studies suggest a trend of increasing healthcare costs for childhood UTI, but results are not directly generalisable to countries such as Australia and the UK which have a predominantly public medical system.

2.5.2.2 Health care utilisation and costs of paediatric UTI in the UK

Australia and the UK have similar predominantly publicly funded healthcare systems, and two previous UK studies have conducted economic evaluations of the costs of childhood UTI.

The 2016 Diagnosis of Urinary Tract infection in Young children (DUTY) cohort study included a substantial health economics analysis of diagnostic strategies, which modelled the costs of childhood UTI from a National Health Service (NHS) perspective. [31] [206] Short term fourteen day resource use average costs for UTI were reported as £126.95. Average costs were based on data collected for the number of clinical contacts, prescriptions, hospital tests, outpatient consultations, hospital admissions and personal costs following the initial consultation in primary care. Medium and long term modelling, however, was more complex, including evolving and debated data regarding the likelihood of UTI leading to permanent renal disease. The authors acknowledge that “some of the evidence underlying the model was imprecise and potentially biased”, and that “the choice of sampling distribution for some parameters, in particular costs and utilities, was based on convention rather than on primary data, introducing subjectivity into the probabilistic sensitivity analysis”. [31] Though the DUTY modelling was robust, limitations of the underlying data from the literature available to inform long term probabilities may influence the certainty of those results.

The comprehensive 2007 NICE UTI in Children Guideline includes a brief chapter on the economic evaluation of management of UTI, [6] which

summarises and evaluates data from a published 2006 Health Technology Assessment (HTA) on the diagnosis and management of UTI. [207] The HTA included a systematic review to inform their modelling, which identified only one paper from the US found to be of limited relevance to the UK NHS system. The NICE 2007 Guideline authors also note concerns that “due to the use of highly questionable assumptions, the HTA model does not estimate the likely cost-effectiveness of specific management strategies for UTI in children.” The NICE Guideline attempted to develop a model to evaluate the cost-effectiveness of UTI diagnosis and management over the short term. However this was not possible as the guideline authors found that many data for the clinical effectiveness of relevant diagnostic strategies was of poor quality or unavailable, and this uncertainty would have led to highly speculative results.

The 2017 update of the NICE Guideline includes limited further economic evidence, but does include additional recommendations for the use of urine dipstick testing for children under 3 years of age, based on evidence of cost-effectiveness of this strategy. [186] The 2017 NICE Resource Impact Report for Urinary Tract Infection in Under 16s stated that 245,000 young children aged 3 months to 3 years will present to medical care in England with symptoms of UTI annually, from the assumption that this will occur in 13.2% of children in this age group. [208] The report estimated the costs of initial diagnosis and treatment of UTI to be £43.25, based on the costs of dipstick microscopy, culture and antibiotics. The report estimates annual savings of £870,000 to £7,833,000 per year in England could be achieved from routine use of urinary dipstick screening, by reducing the number of unnecessary pathology tests and antibiotics needed for infants and children aged 3 months to 3 years with suspected UTI. [208]

Though very limited economic evidence is available, these studies indicate that strategies to optimise the initial investigation of suspected UTI have the potential for significant cost savings in the UK health system.

2.5.2.3 Health care utilisation and costs of childhood UTI in Australia

Costs data for childhood UTI in the Australian healthcare system is very limited.

A 1997 study in the state of New South Wales (NSW) reported 1203 annual paediatric admissions for UTI at an estimated cost of $1.7 million, [209] reflecting a cost of $1413.13 per admission.

More recent published data is not available.

2.5.2.4 Summary of healthcare system costs of childhood UTI

Childhood UTI is recognised as a significant cause of healthcare utilization and expenditure, though there is a lack of recent data to accurately characterise costs. Developing cost-effective strategies to evaluate and treat childhood UTI is recognized as a research priority. [205]

Some studies identified delayed, inappropriate and unnecessary investigations and treatments as likely drivers of increased healthcare costs. Timely and accurate diagnosis of UTI, and targeted outpatient antibiotic therapy, have been identified as avenues to reduce costs. [205] This optimal management is contingent on collection of a reliable urine sample.

The collection of a urine sample requires resources and time, both from a patient and clinician perspective. Collecting a urine sample therefore incurs costs, both for sample collection and subsequent laboratory processing. While the costs of laboratory analysis and antibiotic treatment are relatively fixed, the costs of urine sample collection are potentially modifiable.

2.5.3 Potential cost savings from optimal urine sample collection

Despite urine samples being required in so many young children, the exact costs of sample collection are not known, the most cost-effective collection method is not known, and cost saving strategies have not been studied

directly. A specific literature review identifying this knowledge gap is included in Chapter 6 of this thesis.

One study has evaluated a strategy which could reduce the costs of urine sample collection for young children, though this was not the primary focus of the study. A two stage process for urine sample collection, using initial urine bag collection for screening dipstick testing and subsequent catheter confirmation of positive screening results, was studied in the US ED setting. [210] The intervention reduced catherisation rates from 63% to 30%, with no increase in the ED length of stay. The approach seems promising, however catheterisation is not practical in all settings, and the costs of this care which may include additional staff and resource use were not evaluated.

Optimal urine sample collection has further potential cost benefits beyond the actual collection process itself. This includes reductions in unnecessary and untargeted treatment, and avoidance of morbidity from missed, delayed and misdiagnosis. Minimising sample contamination can reduce an unnecessary cascade of treatment and follow-up for false positive culture results.

Urine collection methods therefore represent an ideal opportunity to find cost savings for this common childhood condition. Understanding the costs and cost-effectiveness of urine sample collection is therefore the second main research aim reported in this thesis, and is evaluated further in Chapter 6.

2.6 CHILDHOOD UTI IN THE PRIMARY CARE SETTING

"Urinary tract infection (UTI) in young children often presents with non-specific symptoms and obtaining a urine sample from those who are acutely unwell is challenging.

Sampling rates are generally lower than recommended, and it has been estimated that up to half of children with UTI in primary care may not be diagnosed when first consulting."

Butler et al (2015) [211]

2.6.1 Evaluating and managing childhood UTI in primary care

In Australia, primary care services play a central role in the delivery of healthcare to children, and many parents will seek initial care for their child in primary care for conditions such as unexplained fever. [5] There are many practical differences between hospital and primary care healthcare settings. For children with unexplained fever or suspected UTI, these differences may directly and indirectly influence how clinicians choose to collect urine samples for young children with potential UTI, and manage suspected and confirmed infections.

When evaluating a child with suspected UTI or unexplained fever in the primary care setting, considerations for selecting the method or urine sample collection may include:

- Time
- Physical space
- Clinician training and experience
- Equipment availability
- Parental preferences and perceptions

As reflected in guideline recommendations from countries where primary care is predominantly provided by general practitioners, non-invasive collection methods may be considered more practical in the primary care setting. [186] The equipment and clinician training required to perform catheterisation or SPA may also not be available in all primary care settings. [104 190]

Access to tests and investigations is another important factor. The hospital setting provides more immediate access to these pathology, laboratory and radiology services. For young children with unexplained fever, this may include onsite access for blood tests which may suggest if the aetiology is more likely viral or bacterial, such as a full blood count. This may also include

other investigations looking for the focus of the fever, such as a chest x-ray to look for pneumonia. These results may assist the clinician in deciding if collecting a urine sample is more or less important.

Treatment options may also be greater in the hospital setting. This may include the option of IV antibiotic therapy if the child is more unwell, or IV fluid therapy if the child is significantly dehydrated or not tolerating oral intake.

2.6.1.1 Impact of the primary care setting on choice of urine collection method

These differences between the hospital and primary care settings can clearly influence how, when and where a urine sample is collected, as well as subsequent management if UTI is considered likely. Understanding the impact of the primary care setting on clinician's choice of urine sample collection methods, and the barriers and enablers to collection, is the third main research aim reported in this thesis and is explored and studied further in Chapter 7.

2.7 SUMMARY & JUSTIFICATION FOR PRESENT RESEARCH

Childhood UTI is one of the most common bacterial infections of childhood. If unrecognised and untreated, serious complications can occur. Many childhood infections have been diminished or even eliminated through improvements in diagnostic or therapeutic advances. However UTI remains a stubborn foe which has seen few advances in management, alongside some new challenges such as increasing antibiotic resistance.

Childhood UTI cannot be diagnosed without a urine sample. The clinical signs of UTI are often non-specific and overlap with many common viral infections, especially in younger pre-continent and pre-verbal children. These young children are also the most at risk of complications such as urosepsis and meningitis. Therefore many febrile children require evaluation for potential UTI, by collecting a urine sample to diagnose or exclude the infection.

Collecting urine from a young pre-continent child is challenging. This is a problem regularly encountered by clinicians in general practice, paediatrics and emergency medicine. Several urine sample collection methods exist, but all have limitations. Non-invasive methods such as urine bags and clean catch can be time-consuming or contaminated. Invasive methods require equipment and expertise which is not broadly available, and cause pain and distress to the child. These limitations and difficulties can lead to suboptimal care with untargeted, unnecessary or delayed treatment. There is significant variation in international guideline recommendations, and parental and clinician preferences, for the preferred collection method. Australian and UK guidelines recommend clean catch as the first line collection method, for which adequate time and space to attempt collection is required. There is a clear need to optimise the urine sample collection methods used for young children.

Childhood UTI is expensive at a healthcare system level. Improving the efficiency and effectiveness of urine sample collection would not only benefit patients, but also could reduce costs. As collecting urine from young febrile children is very commonly required, even modest cost savings are likely to be significant in the aggregate.

Finally, a large proportion of children with unexplained fever and suspected UTI present to primary care. There are significant differences between the resources available to collect urine samples and manage suspected UTI for these children in primary care compared to hospital and specialist settings. Therefore it is important that first line UTI investigation and management strategies are practical, and suited to the primary care setting.

Chapter 3 AIMS AND HYPOTHESES

3.1 PREAMBLE

The preceding background chapter has highlighted that collection of urine samples is a crucial and unavoidable part of the diagnostic work-up for young pre-continent children with potential UTI, but collection processes remain challenging.

Improving urine sample collection would greatly improve the quality and acceptability of care for the many children worldwide who are evaluated for potential UTI. Urine sample collection is required for all of these children, despite the fact that only a proportion of these children will actually have a UTI and require further management. Consequently, for all children being evaluated for UTI the greatest impact is likely to come from improving what gets done the most, which is collecting the initial urine sample.

Therefore, a particular research priority which is recognised in the literature is to improve non-invasive collection methods. [15] These methods are used most broadly and are applicable in all clinical settings, including primary care and resource-limited settings. Clean catch is a commonly favoured non-invasive method, but it's clinical utility is limited by its potentially time-consuming nature, failure rate and contamination. Improving the clean catch collection method would have many benefits for patients, families, clinicians and health services.

The overall objective of this doctoral research was to improve the care of young pre-continent children being evaluated for potential UTI, by improving non-invasive urine sample collection for these children.

The scope of the research was limited to pre-continent children, which typically includes infants and young children up to 1-2 years of age.

To address this objective, the thesis has four parts relating to four inter-related research aims. Different methodologies are used in each part to address each specific aim, including clinical research, health economic evaluation, qualitative research, and knowledge translation.

This chapter describes the four specific aims, and corresponding research questions and hypotheses, with a brief overview of the methods and studies used to address each aim. As each aim was addressed differently, a more detailed account of the methods is included in the subsequent chapters dedicated to each study.

Methods followed internationally recognised reporting guidelines as recommended by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network. [212] EQUATOR is an international initiative to improve the reliability of published health research literature through transparent and accurate reporting and use of robust reporting guidelines. The relevant guidelines and checklists are detailed in subsequent chapters.

3.2 THESIS AIMS, HYPOTHESES, OVERVIEW OF METHODS

3.2.1 Part 1: Clinical Research

Quick-Wee: an improved non-invasive urine collection method

Primary Aim

I. To develop a simple voiding stimulation method for faster and more effective non-invasive urine sample collection for young pre-continent children.

Secondary aims

I. For the method to be pragmatic and suited for use in primary care and low-resource settings.

II. For the method to be gentle for children and acceptable for use by parents and clinicians.
III. For the method to reduce the contamination of clean catch urine samples.
IV. To provide definitive evidence for the method with a robust randomised trial.

Hypothesis

Young children have involuntary voiding reflexes which can be targeted to trigger urination for urine sample collection.

Methods

I. Pilot study of the novel Quick-Wee voiding stimulation method.
II. Co-authored baseline study of existing clean catch collection method practice.
III. Protocol for a randomised trial of the Quick-Wee method.
IV. Randomised trial of the Quick-Wee method.

3.2.2 Part 2: Health Economic Evaluation

Liquid Gold: costs and cost-effectiveness of urine collection methods

Primary Aim

I. To determine the costs and cost-effectiveness of commonly used urine sample collection methods for young pre-continent children in the hospital setting.

Secondary Aims

I. Include in the analysis the costs of initial sample collection, as well as projected costs for collecting a definitive sample incorporating the progressive dipstick screening, culture, contamination and patient

progress that are used by clinicians to reach a conclusive clinical decision.

II. To compare the cost and cost-effectiveness of the new Quick-Wee voiding stimulation method to existing collection methods.

III. To estimate the potential health service cost savings from cost-effective sample collection at a hospital and national level.

Hypothesis

Urine sample collection costs are influenced by the staff, equipment and health service resources used for sample collection as well as the time taken, success and contamination rate of the method.

Methods

I. Health economic evaluation of common urine collection methods used for pre-continent children, adopting a health service perspective with the ED as the primary service provider. The analysis includes a literature review, process mapping, clinician survey, costs analysis, construction of a modelled probabilistic decision analytic model, and sensitivity analysis.

3.2.3 Part 3: Qualitative Research

What's The Catch: what are the barriers and enablers to urine sample collection in the primary care setting?

Primary Aim

I. To explore and characterise the barriers and enablers to collecting urine samples from young pre-continent children in the Australian primary care general practice setting.

Secondary Aims

I. To synthesise these findings to highlight the challenges of childhood UTI diagnosis in the primary care setting.
II. To inform future guideline recommendations for urine collection strategies that are suited to the primary care setting.
III. To inform, guide and direct future research in this field, targeted at developing urine collection strategies suited specifically to young children in the primary care context and setting.

Rationale

The primary care setting is different to the hospital setting, which may influence clinical practice. While qualitative research is not designed to test hypotheses, the rationale for this study is to understand the unique barriers and enablers for urine sample collection that exist in the primary care setting, and how the nature of the primary care setting may influence clinician preferences for collection methods.

Methods

I. Qualitative study with semi-structured interviews of doctors and nurses in Australian general practices.

3.2.4 Part 4: Knowledge Translation

Primary Aim

I. Incorporation of the Quick-Wee method into clinical practice guideline recommendations.

Secondary Aims

I. To raise awareness of the Quick-Wee method amongst parents, caregivers, clinicians, researchers and policy makers.
II. To produce targeted education resources to facilitate use and uptake of the Quick-Wee method.

Rationale

Disseminating research findings into a broad range of clinical and policy settings will facilitate knowledge translation.

Methods

I. Revision of the Victorian statewide UTI clinical practice guideline.
II. Targeted consumer education resources for clinicians and caregivers.
III. Targeted clinical review article publications to highlight the clinical utility of the new Quick-Wee method.
IV. Scoping of uptake of the Quick-Wee method into guidelines.

Chapter 4 QUICK-WEE: PILOT STUDY

"The collection of urine from young children is essential, frustrating and upsetting for both the child and the carer. There is currently no ideal solution that addresses the problems of speed, convenience, effect on the child, accuracy and risk of complications.

The clean catch sample is commonly used as a non-invasive, low contamination compromise. However, this often leaves patients and parents with a distressingly long wait.

In our view, instantly available clean catch samples would be the ideal collection method."

Davies et al (2008) [127]

4.1 OVERVIEW

This chapter describes the first part of the thesis research, the development of the Quick-Wee voiding stimulation method.

Sections 4.2 - 4.4 explain the rationale for using voiding stimulation methods in young pre-continent children, and the aims and hypotheses of this chapter.

Sections 4.5 - 4.7 evaluate the physiological basis for using cutaneous stimulation to trigger voiding. Following a targeted literature review, previously studied voiding stimulation methods and the limitations of these methods and trials are evaluated. This highlights the important knowledge gap that this research targets, and provides the basis for developing the novel Quick-Wee voiding stimulation method.

Section 4.8 describes the novel intervention, and evaluates feasibility in a pilot study, which includes the study methods, results, and published paper.

Section 4.9 evaluates existing practice in a co-authored baseline observational study of the standard clean catch collection method.

Sections 4.10 summarises the potential benefits of the new Quick-Wee method, justifying a larger and more definitive subsequent trial.

PAPER 2: PILOT STUDY

The published pilot study (Paper 2) forms part of this chapter:

2. **Kaufman J**, Tosif S, Fitzpatrick P, Hopper S, Donath S, Bryant P, Babl F. QuickWee: a novel non invasive urine collection method. *Emergency Medicine Journal* 2017 Jan;34(1):63-64. doi: 10.1136/emermed-2016-206000

The co-authored baseline study described in this chapter is also included in Appendix 11.1.6 of this thesis:

Tosif S, **Kaufman J**, Fitzpatrick P, Hopper S, Hoq M, Donath S, Babl F. Clean Catch Urine Collection: Time taken and diagnostic implication. A Prospective Observational Study. *Journal of Paediatrics & Child Health* 2017 Oct;53(10):970-975. doi: 10.1111/jpc.13595

4.2 RATIONALE

Urine collection from young pre-continent children can be a difficult and frustrating process. Children who are not yet toilet-trained, unlike older children and adults, cannot void on demand to provide a sample.

Current collection methods are described previously in Chapter 2. These include non-invasive methods (waiting for the child to pass urine spontaneously and opportunistically collecting a sample with a urine bag, nappy pad or clean catch of the urinary stream) and invasive methods (extracting urine directly from the bladder with a catheter or needle). All of these current collection methods have limitations, as described in Chapter 2.

Non-invasive methods are often favoured for their convenience. They avoid the pain and distress caused by invasive procedures, and do not require specialist equipment and expertise to perform. But waiting for a young child to void spontaneously can take a long time. In clinical settings, this can be inconvenient and impractical. The commonly favoured clean catch method requires constant vigilance from the person designated to catch the sample, as the child may void at any moment. For the parents and carers of a sick child, this can be challenging and demanding. Clean catch attempts are not always successful in practice.

If there was a way to trigger children to void when a sample is required, this could overcome many of the limitations of existing non-invasive collection methods. Young children are not born with volitional control over voiding, and rely on involuntary bladder reflexes to initiate urination. These bladder reflexes could potentially be targeted to stimulate voiding.

Difficulties with urine sample collection from young pre-continent children are common and frustrating. Improved non-invasive urine collection would represent a major advance in care for these children. A simple, gentle and practical method would have broad applicability for many children across many settings. As described previously, the literature explicitly identifies this as a recommended area for research, with US guidelines stating “the development of techniques that would permit an alternative to invasive sampling and culture would be valuable for general use.” [15]

Therefore for the first area of research in this thesis, the doctoral candidate developed a novel voiding stimulation method to improve the speed and success of non-invasive urine sample collection for young pre-continent children, and tested its feasibility in a pilot study.

4.3 AIMS

4.3.1.1 Primary Aim

The primary aim of this pilot study was:

I. To develop a simple voiding stimulation method for faster and more effective non-invasive urine sample collection for young pre-continent children.

4.3.1.2 Secondary Aims

The secondary aims of this pilot study were:

I. For the method to be pragmatic and suited for use in primary care and low-resource settings.
II. For the method to be gentle for children and acceptable for use by parents and clinicians.
III. For the method to reduce the contamination of clean catch urine samples.
IV. To evaluate the feasibility of using the method in a clinical setting.

In addition, a planned co-authored baseline study of current practice was concurrently performed, with the secondary aims:

V. To describe the outcomes of existing practice using the standard clean catch collection method.
VI. To use this data to perform sample size calculations for a subsequent randomised trial.

4.4 HYPOTHESES

As described in Chapter 3, it was hypothesised that:

I. Young pre-continent children have involuntary bladder voiding reflexes which can be targeted with gentle cutaneous stimulation, to trigger urination for urine sample collection.

The doctoral candidate hypothesised that a voiding stimulation method, compared to existing practice with the clean catch urine collection method in young pre-continent children, would:

II. Increase the rate of voiding urine.
III. Increase the rate of successful urine sample collection.

The doctoral candidate also hypothesised that the voiding stimulation method would:

I. Be feasible to perform in a busy clinical setting.
II. Reduce the contamination rate of samples collected.

4.5 CONCEPTUALISATION OF THE NOVEL METHOD

4.5.1 Characteristics of an ideal collection method

Current non-invasive urine collection methods trade between convenience and contamination, although all non-invasive methods rely on waiting for the child to void spontaneously, which can be time-consuming.

As discussed in Chapter 2, urine bags and nappy pads may be favoured in some settings due to their perceived convenience. Though waiting for urination may take a long time, these methods do not require constant vigilance from clinicians or parents. However urine bags have a contamination and false positive rate of approximately 50%, [130] and urine pads may have even higher contamination. [139] This significantly limits their use in diagnosing UTI, and many guidelines specifically recommend against the use of bag urine samples for culture. [12 16 23 104 187 189 190]

Therefore clean catch is often the favoured non-invasive collection method, due to its substantially lower contamination rate. [3] It is often the preferred collection method for clinicians, [142] and often recommended by clinical practice guidelines. [6 64 187] The main limitations of the clean catch method are its time-consuming nature, the constant attention required during collection attempts, and suboptimal collection success rate. [127 136] Improving these deficits with clean catch collection would greatly increase the clinical utility of

non-invasive collection, and it has been stated in the literature that “instantly available clean catch samples would be the ideal collection method”. [127]

Improved clean catch collection would ideally be quick and simple for parents and clinicians, and gentle for the child, with effective collection of a reliable sample.

4.5.2 Anecdotal observations and initial hypothesis

As a trainee doctor, I had noticed that some young children, particularly babies and infants, seemed to void spontaneously during preparation for urine sample collection procedures. The first step in this preparation is to remove the child’s nappy, which exposes the lower abdomen and pelvis to the colder external air. The next step is to clean the perigenital skin with cleaning fluid, typically either sterile water, saline or chlorhexidine solution. Repeated incidental observations during my clinical work suggested that voiding was most likely to occur shortly after the cleaning fluid was applied to the skin of the perigenital or suprapubic region.

Similarly, many parents will have observed that young children often void during nappy changes, or with cleaning of the perigenital area with baby wipes. The cold and wet cutaneous stimuli that occur during nappy changes are similar to those that occur during perigenital cleaning prior to urine sample collection procedures.

I wondered if this could somehow form the basis of a more formal method of collecting urine samples. When performing catheter or SPA procedures it became my routine practice to have a spare specimen jar and dedicated urine catcher at the ready, in case a clean catch sample could be collected opportunistically during the cleaning. Sometimes the child would void during cleaning, a sample was caught, and the invasive collection procedure was no longer required.

These anecdotal observations led me to hypothesise that cleaning the perigenital and suprapubic skin was triggering involuntary voiding in these infants, via a reflex mechanism, induced by the cutaneous cold and wet sensory stimulation.

However the plural of anecdote is not data, and so in these observations was the genesis of the research idea that led me to conceptualise and develop the Quick-Wee method, and to embark on this doctoral thesis to test the hypothesis.

4.5.3 Principles of voiding stimulation methods

A voiding stimulation method aims to induce involuntary bladder voiding so a urine sample can be collected non-invasively. This has the potential to improve the speed and success of non-invasive urine sample collection.

The ideal voiding stimulation method would be effective and also simple to perform. Any equipment required should be commonly available. The method should not require specialist training so that it can be performed by non-experts, or even parents and carers. Crucially, the method should be gentle to children. A relatively short intervention duration would be appropriate for busy clinical environments. These considerations would ensure that the method is suited to any clinical context, including hospitals, ED, general practice and resource-limited settings.

At the time of conceptualising the new method, I was not aware of any voiding stimulation methods being actively used in clinical practice.

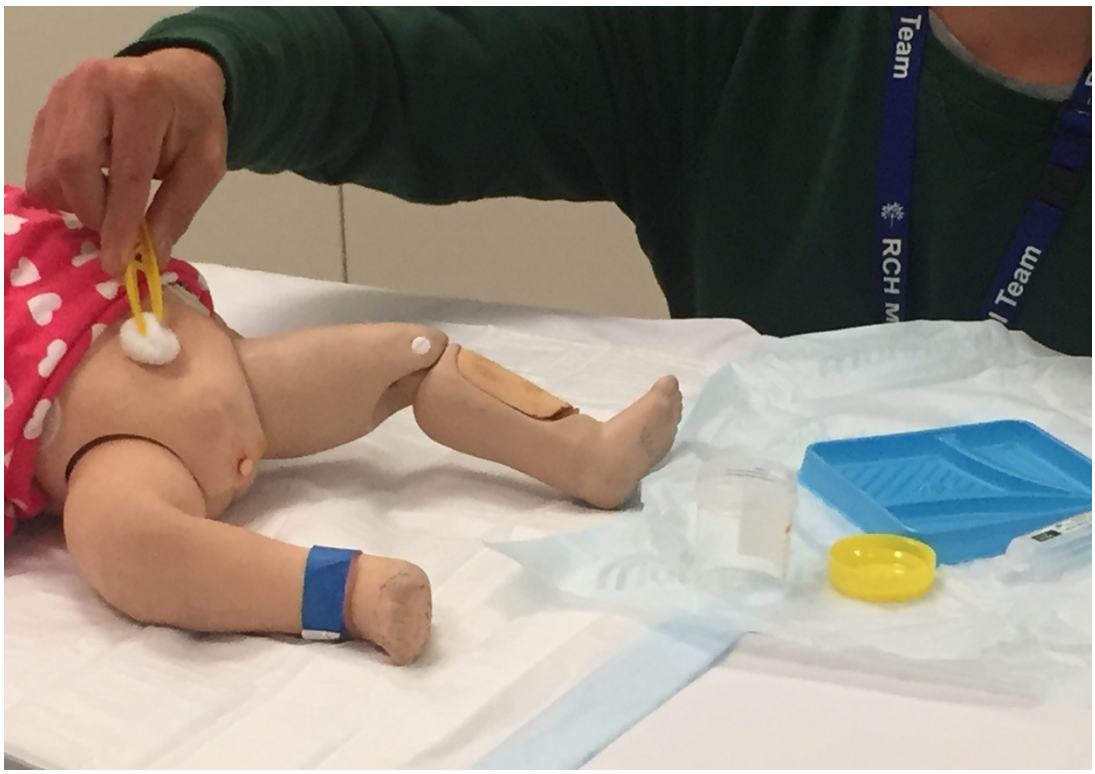
4.5.4 Quick-Wee: a novel voiding stimulation method

As described above, anecdotally, many young children void spontaneously with cleaning of the perigenital and suprapubic skin prior to urine collection procedures. Key elements of this anecdotal observation are:

- The stimulation is applied using fluid soaked gauze rubbed onto the skin, which provides mechanical cutaneous sensory stimulation
- The fluid used is typically colder than the skin, which provides thermal cutaneous sensory stimulation

This led to the conceptualisation and development of the Quick-Wee voiding stimulation method (Figure 6).

Figure 6: Quick-Wee voiding stimulation method



The Quick-Wee method is performed as follows:

- Standardised cleaning of the perigenital area is performed for a duration of 10 seconds (routine practice)
- Saline fluid is used to soak a piece of gauze
- Cutaneous stimulation is applied to the suprapubic area using the wet gauze held by plastic forceps
- The stimulation is applied using gentle circular motions
- The stimulation is applied for up to five minutes

- The stimulation is ceased if the child voids urine and a sample is collected in a specimen jar (successful collection), an adverse event occurs, or the five minute intervention period is reached

A five minute intervention duration was chosen to be practical for busy clinical settings.

4.5.4.1 Equipment

The equipment required consists only of a standard basic dressing pack containing plastic forceps and gauze, and a standard 10 millilitre (ml) saline ampoule. These materials are low-cost and readily available in clinical settings, and could be easily substituted in resource-limited environments. Saline was chosen as the intervention fluid for practical reasons, as it is commonly used in clinical settings, however it is likely that other fluids would have a similar effect.

4.5.4.2 Operator training

The Quick-Wee method is simple to perform and does not require specialised expertise or experience. It would not require specific training beyond the method being briefly described or demonstrated. It could be easily performed by any clinician, or by parents and carers.

4.5.4.3 Risk of adverse events

The Quick-Wee method is non-invasive, gentle and would not be expected to cause any significant discomfort or adverse reactions in children.

4.5.4.4 Mechanism of action

The Quick-Wee method utilises mechanical and thermal stimulation to the perigenital and suprapubic skin to trigger voiding. The proposed mechanism of action is that this stimulation elicits an involuntary cutaneous voiding reflex. The presence of such reflexes would provide a physiological basis for the proposed voiding stimulation method. This theory led to a search of the literature for evidence of cutaneous voiding reflexes from animal or human studies.

4.6 EVIDENCE OF NEWBORN CUTANEOUS VOIDING REFLEXES

4.6.1 Newborn reflexes

Newborn reflexes, also known as primitive reflexes, are complex stereotypical patterns of movement elicited by a specific sensory stimulus. [213] They may be elicited from as early as 25 weeks gestation and are fully present in term babies at birth. [213]

A well known example is the newborn sucking reflex, where a baby will suck reflexively in response to having an object placed in its mouth. Another example is the rooting reflex, where a baby will turn its head towards a cutaneous stimulus on its cheek. These reflexes enable the newborn baby to breastfeed. Other newborn reflexes include the Moro, palmar grasp, plantar grasp, asymmetric tonic neck, step and crossed extensor reflexes. [213 214]

Newborn reflexes diminish with age, corresponding with maturation of the central nervous system, development of voluntary motor control and emergence of motor cortex inhibition. The expected age of disappearance for each reflex varies, but most are absent beyond 6 or 12 months. [213 214] The presence of these reflexes beyond infancy is abnormal, but may occur in neurological conditions such as cerebral palsy and brain injury.

Newborn involuntary cutaneous voiding reflexes are the proposed mechanism for the Quick-Wee method.

4.6.2 Cutaneous voiding reflexes: animal models

There is evidence in the literature for animal models of perigenital cutaneous voiding reflexes. It has been observed that the newborns of some animal species do not void voluntarily in their early life postnatal period, suggesting bladder activation at this time is under involuntary reflex control.

Studies in rat pups have demonstrated that their voiding in early life requires activation of perigenital-bladder reflexes, triggered by the mother licking the perigenital region of the pup. [215] [216] Further, maternal separation in the postnatal period leads to complete urinary retention, [217] [218] and volitional voiding begins only after 3 weeks of life. [219] Similar findings have been noted in other animal species including dogs and cats. [220] [221]

It has also been demonstrated that electrical and mechanical perigenital stimulation can induce or inhibit bladder activity and voiding in cats with chronic spinal cord injury (SCI). [222] These findings are from a study performed in four adult female cats, one month after surgical spinal cord transection to induce SCI. Electrical perigenital stimulation was applied using sterilized hook electrodes attached to the skin. At lower frequencies (5-7Hz) the stimulation significantly inhibited bladder activity whereas at higher frequencies (20-40Hz) induced excitatory bladder contraction. Mechanical perigenital stimulation using a cotton swab to lightly stroke the perigenital skin also induced an excitatory bladder contraction. Further studies have shown that bladder contraction can also be induced in cats with an intact neuroaxis via cutaneous stimulation by scratching or electrical stimulation. [223]

Demonstration of these excitatory perigenital-to-bladder voiding reflexes in animals suggests a physiological basis for proposed non-invasive voiding stimulation methods in humans.

4.6.3 Cutaneous voiding reflexes: proposed human mechanism

The neural pathways involved in control of urination are complex, have significant plasticity in the postnatal period, and are distributed across the brain, spinal cord, and peripheral nervous system.[224] [225]

Toilet training in western culture usually begins from two to four years of age. [224] [226-228] Urinary continence, or the voluntary control of voiding urine, was achieved at a median age of four years in a Swedish longitudinal study. [227] However studies in other populations have found that earlier voluntary control

of urination is possible with earlier toilet training. A smaller Vietnamese longitudinal study found that urinary continence was achieved by two years of age for children who had predominantly commenced toilet training by 6 months. [229] [230] Cultural differences in the toilet training process were also noted, including children rarely wearing diapers, and parents whistling while their child sat on the potty to remind them to void. [230] Before achieving urinary continence, voiding of urine is thought to be involuntary.

Somato-bladder reflexes, similar to the perigenital-to-bladder reflexes noted in animals, are also found in young human infants. [224] [225] These primitive voiding reflexes are likely similar to other newborn reflexes (e.g suck, step, Moro) in that maturation of neural systems occurs, and the reflex response fades in the first year of postnatal life. Voluntary control of urinary continence can subsequently develop. It can be therefore be expected that cutaneous voiding reflexes would be most prominent in the first months of life, and diminish with time. It follows therefore that that voiding stimulation methods would be most effective in the first year of life.

These cutaneous somato-bladder reflexes are the physiological basis for voiding stimulation techniques, which can be used to trigger voiding for urine collection in young pre-continent children.

4.7 LITERATURE REVIEW: VOIDING STIMULATION METHODS

A targeted literature review was undertaken to identify published studies of voiding stimulation methods used in young pre-continent children.

As stated previously, at the time of initially conceptualising the Quick-Wee method, the doctoral candidate was not aware of any published studies of voiding stimulation methods.

Ms Poh Chua, RCH Senior Librarian, provided assistance with designing and refining the literature review strategy.

Databases searched included Ovid Medline, PubMed and Embase. Further targeted searching from reference lists and relevant guidelines was performed. While search terms varied slightly between databases, they effectively focused on the terms “child”, “urinary tract infection”, “urine specimen collection”, “urine specimen collection methods” and “physical stimulation”. Full details of the search strategy and search terms, inclusion criteria and screening process is included in Appendix 11.6.1.

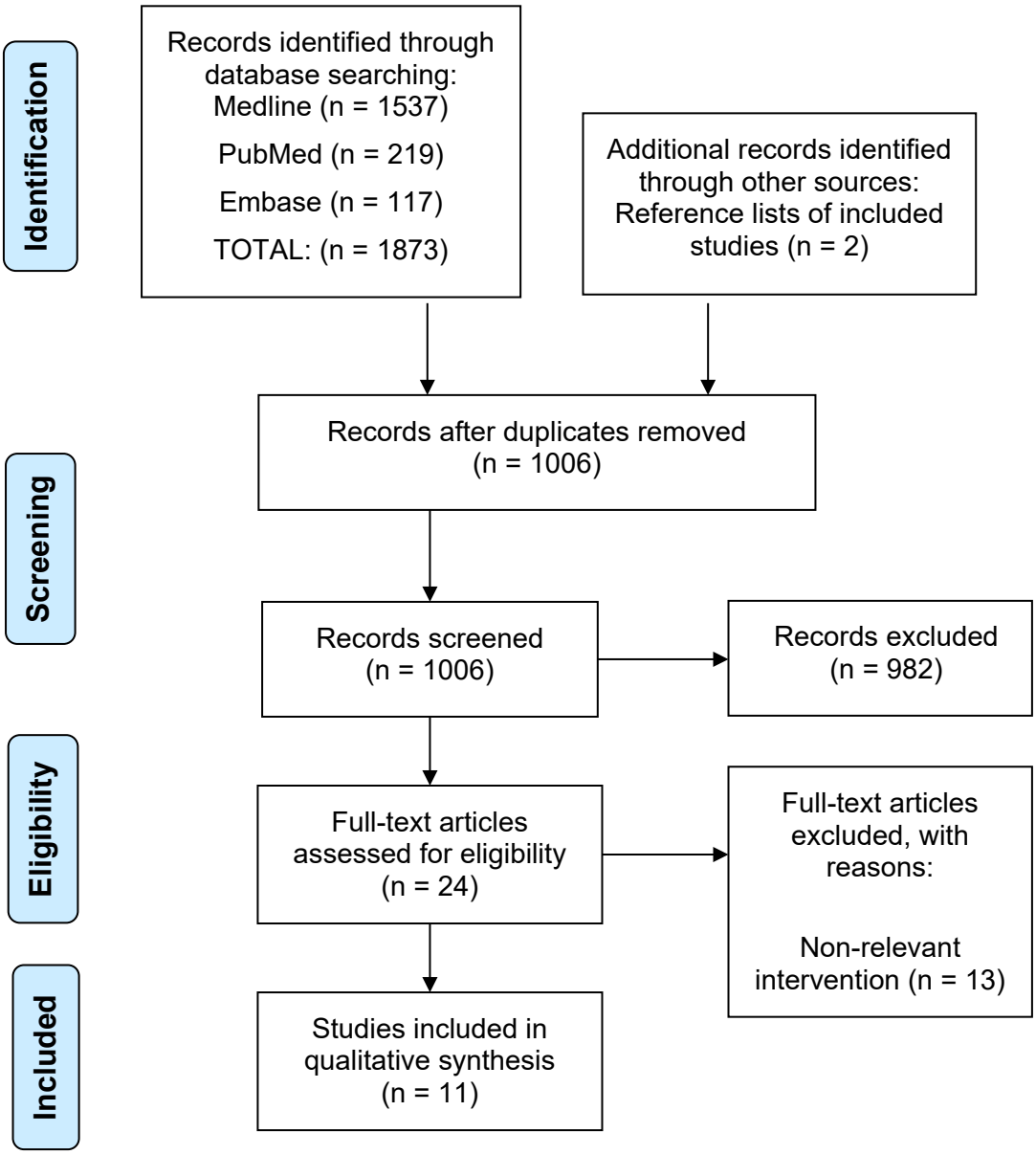
Studies were included in the final evidence summary if they reported any voiding stimulation method used in young pre-continent children (Figure 7).

11 studies of three different voiding stimulation methods were identified:

1. Finger tap method (n=2)
2. Bladder and lumbar stimulation method (n=8)
3. Vibrating bladder stimulation device (n=1)

Figure 7: Voiding stimulation methods: literature search summary

Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) flowchart [231]



4.7.1 Finger tap method

4.7.1.1 Broomhall et al (1985)

The earliest description found in the literature of a voiding stimulation method is a 1985 report in the *British Medical Journal*. [232] Broomhall et al described a "reliable, non-invasive technique for obtaining urine samples from babies", using a lower abdominal finger tapping method.

The authors described tapping firmly above the pubic symphysis in the midline, using two fingers, at a rate of about one tap per second. With tapping and pausing for alternating minutes, the authors reported a success rate of 24 out of 31 babies (77%) passing urine within 10 minutes in the intervention group, compared to 8 of 31 babies (26%) in the control group. No data about the age or sex of the babies is included in this brief one paragraph article.

4.7.1.2 Taylor et al (1986)

In 1986 and also in the *British Medical Journal*, Taylor et al further evaluated the finger tap method described by Broomhall, performing the technique one hour after feeding the baby. [233] Of 154 samples from 133 children aged 1 week to 12 months of age in the study, 105 were obtained by the finger tap method and the remainder by bag collection. There is limited detail reported about the study methods. The authors report that the mean time to collect urine with finger tapping was 5.5 minutes and the longest collection time was 20 minutes. However the collection time was recorded in only 48 of 105 cases (representing 46% of the sample), and although implied, the authors do not explicitly state if collection by finger tapping was unsuccessful for any cases.

4.7.1.3 Summary of finger tap method

The finger tap method is the first voiding stimulation method for young pre-continent children described in the literature, however limited description of study methods makes the utility of findings difficult to assess.

4.7.2 Bladder and lumbar stimulation in neonates

4.7.2.1 Herreros et al (2013)

In 2013, Herreros et al described a “new technique for fast and safe collection of urine in newborns”, in a prospective cohort feasibility study of 80 neonates in a Spanish secondary Neonatal Unit. [234] The authors hypothesised using bladder and lumbar stimulation to obtain clean catch urine samples, similar to techniques used to facilitate bladder emptying for adult patients with bladder dysfunction secondary to multiple sclerosis. [235]

The babies were initially fed according to a prespecified routine which occurred 25 minutes prior to performing the intervention. Babies with poor feeding were excluded. The first operator (a doctor or nurse) then held the baby aloft with legs dangling, suspended under their armpits. The second operator then performed the bladder and lumbar stimulation. A third operator timed the procedure and caught the sample. The stimulation consisted of alternating 30 second periods, first with bladder tapping at a rate of 100 taps per minute, and second with lumbar circular massage (Figure 8). The intervention was performed for up to 5 minutes.

Figure 8: Bladder lumbar stimulation method



Image from Labrosse et al, Pediatrics 2016 (reproduced with publishers permission) [236]

The study had an impressive success rate of 86% for the primary outcome of collecting a urine sample within 5 minutes. No complications beyond infant

crying were noted. The authors note the lack of a control group and the standardised pre-procedure fluid intake as potential limitations of the study.

The findings of the study by Herreros et al were promising, but with some limitations to generalisability. Firstly, the babies had a mean age of 6 days. A method that relies on triggering newborn reflexes would be expected to have higher success in early life and less success in older infants. Also suspending a newborn baby aloft may be much easier than doing so for older and heavier infants. Secondly, few patients in the study were being evaluated for potential UTI. Less than a quarter of the babies had urine collected to screen for infection. Most babies had urine collected for reasons such as jaundice and CMV screening. Babies who have infections such as UTI may be more unwell and less likely to void urine due to their medical state or secondary dehydration and fluid loss. Thirdly, babies with poor feeding or dehydration, or who did not feed according to the pre-procedure specified feeding plan, were specifically excluded. However in clinical practice many of the infants and young children with fever who require evaluation for potential UTI are likely to have suboptimal feeding and some dehydration.

Therefore the young age of patients in the study, exclusion of patients with poor feeding, and low percentage of patients being evaluated for potential UTI, may inflate the success rate of the method in this study compared to typical infants with potential UTI. Several characteristics of the patient population also limit the generalisability of findings, including the young age of the patients, reasons for sample collection and Neonatal Unit setting.

4.7.2.2 Altuntas et al (2015)

In 2015, Altuntas et al evaluated the Herreros bladder-lumbar stimulation method in a randomised controlled trial (RCT) of 127 neonates in a Turkish tertiary Neonatal Intensive Care Unit (NICU). [140] [234] The study used the same feeding and stimulation intervention as Herreros et al. Babies in the control group were held suspended by their armpits but without additional stimulation. Three operators (specifically trained doctors or nurses) performed the intervention. Infants with poor feeding and dehydration were again excluded.

The Altuntas RCT found a success rate for urine sample collection within 5 minutes of 78% in the intervention group compared to 33% in the control group. The authors reported a sample contamination rate of 24% in the intervention group compared to 29% in the control group. No adverse events were reported beyond infant crying. While randomisation was a strength of the Altuntas study, similar factors to the original Herreros study limit generalisability including a patient population exclusively from a tertiary NICU setting with a mean age of 7.5 days, a minority of patients being investigated for fever or potential UTI, and exclusion of babies with poor feeding.

4.7.2.3 Nepal et al (2016)

In 2016 Nepal et al evaluated the Herreros bladder-lumbar stimulation method in a prospective cohort study of 100 neonates with a mean age of 1 day old. [237] Patients with poor feeding or dehydration were again excluded. Using the same feeding and stimulation method as the original Herreros study, a success rate for the intervention of 91% in a 4 minute timeframe was reported, with no complications beyond infant crying. Interestingly in this study the authors noted that all urination occurred during the suprapubic bladder tapping, rather than during lumbar massage.

4.7.2.4 Summary of bladder lumbar stimulation in neonates studies

Results from these studies of the bladder-lumbar method in the neonatal setting are promising, with success rates for neonates of 78-91% within 5 minutes, although only one study was randomised.

However generalisability to infants and young children being evaluated for potential UTI is limited, for reasons including:

- Urine collection in these studies was performed predominantly for other indications, such as jaundice and CMV screening.
- Babies with poor feeding and dehydration were specifically excluded though many children with UTI demonstrate these features. Excluding these participants is likely to increase the success of the intervention.

Additionally, the bladder-lumbar stimulation method may be less practical to perform in older pre-continent infants and young children. As described above, the method requires 2-3 operators to perform and requires suspending the baby aloft by the armpits, which may be less feasible in older and heavier infants, and therefore also less successful in older infants.

At the time of commencing candidature in 2015, only the original Herreros 2013 study had been published, and no studies had been published evaluating the use of the bladder-lumbar stimulation method outside the neonatal setting.

4.7.3 Bladder and lumbar stimulation in infants and children

Further studies evaluating the bladder-lumbar stimulation method have subsequently been conducted in older infants and young children. These studies were published after the doctoral candidate commenced candidature.

4.7.3.1 Herreros et al (2015)

In 2015 Herreros et al evaluated their own previously described bladder-lumbar stimulation method, [234] in a Spanish ED setting, for infants less than 90 days old presenting with fever without focus. [141] Paired samples were collected by clean catch with voiding stimulation and catheterisation, to compare contamination rates. Infants with poor feeding were again excluded. Of 131 recruited patients, only 60 had paired samples, 35 underwent direct voiding only and 28 underwent catheterisation only. The success rate of infants undergoing bladder-lumbar stimulation was not specifically reported, but could be calculated from the data in the published paper as 73% (95/131), without knowing if these samples were collected within a 5 minute intervention period or not.

Contamination was defined as “mixed bacteria growth or growth of one or more non-pathogenic bacteria (organisms such as Lactobacillus species, coagulase negative Staphylococci and Corynebacterium species), irrespective of the colony count”. Contamination of samples obtained by bladder-lumbar

stimulation was lower (5%) than the contamination rate of catheter specimens (8%). Previous studies have generally found the opposite, that catheterisation has lower contamination than clean catch samples. [3 238] Therefore this study suggests that contamination of clean catch samples could possibly be reduced using voiding stimulation methods.

4.7.3.2 Tran et al (2016)

In 2016, Tran et al conducted a prospective cohort study evaluating the bladder-lumbar stimulation method in pre-ambulant young children less than 2 years of age in a French tertiary paediatric ED. [239] Children with poor feeding or hydration were not specifically excluded, but children with abnormal vital signs were. Tran et al used the same bladder-lumbar stimulation intervention as previously described, but instead of a 5 minute intervention period, used two 3 minute intervention periods, separated by a 30 minute period where the child was offered further oral intake to improve hydration. The intervention was performed by one of four specific physician investigators, with two assistant nurses to hold the child and attempt catching the sample. 204 children met the eligibility criteria for the study and were consented for inclusion, of which 142 were included in the per protocol analysis. The authors report a headline success rate of the intervention of 55.6% during either of the two 3 minute intervention periods from their per protocol analysis.

However, an important methodological consideration for these findings is how the authors conducted their per protocol analysis. The authors state that "infants who voided in the sterile bag after the first attempt or infants for whom the second attempt could not be carried out (parental refusal, leaving the emergency room, or worsening of clinical status) were excluded". Therefore the primary outcome calculation excluded 62 enrolled children including 51 who voided in a urine bag during the 30 minute period between the two 3 minute stimulation periods, 8 children who left the ED during this time, and 3 whose parents refused a second attempt. Therefore only 142 children were included in the primary analysis. It could be argued that the 62 children who were excluded after enrolment should have been included in an intention-to-treat analysis and had in fact failed the intervention. From the published data

reported, the success rate of the intervention by an intention-to-treat analysis would be 39% (204 infants included in the study, 79 urine samples collected during either of the 3 minute intervention periods). In the published paper the authors do not report a true intention-to-treat analysis, although do state in the discussion that “we expected that our study protocol would not be able to be respected in some patients. Indeed, 51 infants were excluded from the analysis because they urinated in sterile bags before the second attempt. If all patients from whom urine samples were collected (n = 193) are included in the analysis, an alternate calculation of the success rate is 40.9%”.

Tran et al also reported on several new findings from their regression analysis, relevant to using the method in older infants and children. The study found that success decreased with increasing age and weight, reporting that “the success rate decreased with age, from 88.9% in newborns to 28.6% in infants older than 1 year (p = 0.0001), and with weight, from 85.7% for infants weighing less than 4 kg to 28.6% for infants weighing more than or equal to 10 kg (p = 0.0004).” Tran et al also found that infant distress and a heavier weight of the infant were associated with failure to void with the voiding stimulation intervention.

4.7.3.3 Labrosse et al (2016)

In 2016 Labrosse et al conducted a further prospective cohort study, evaluating the bladder-lumbar stimulation method in a Canadian tertiary paediatric ED. [236] The study included 126 infants aged under 6 months, with the intervention performed by the principal investigator or specifically trained research nurses. The intervention was performed as described by Herreros in the original study, [234] but “all infants were given the possibility to feed during a 20-minute period” rather than mandatory feeding prior to the intervention. Infants with poor feeding or dehydration were included in the study, unless haemodynamically unstable, although only 6% of the study participants had low oral intake before the procedure.

The success rate of the intervention within 5 minutes was 49%, and the rate of sample contamination was 16%. In the regression analysis, age group was

a strong predictor of success with the intervention more likely to be successful in younger infants, while sex of the child, low oral intake, and having urinated within the preceding hour did not predict success.

4.7.3.4 Valleix-Leclerc (2016)

In 2016 Valleix-Leclerc also conducted a prospective cohort study of the bladder-lumbar stimulation method, [240] in three French paediatric EDs. The study included 48 pre-continent children over one month of age, with the intervention performed by general nursing staff from the departments rather than dedicated research staff. 3 operators were required (2 nurses and a student) for a 5 minute intervention as previously described by Herreros et al. [234]

The success of the intervention in this study was 27%. Success was more likely with younger infants and less likely with heavier infants, consistent with the previously described studies. Additionally, the study found there were difficulties maintaining the position of the child due to weight for 48% of participants, and struggling children reported by nursing staff for 28% of participants. The only complications noted were crying and redness of the skin.

4.7.3.5 Nikam et al (2017)

In 2017 Nikam et al evaluated the bladder-lumbar stimulation method in 76 infants less than 6 months of age from a convenience sample in an Australian ED. [241] Infants with dehydration or who were clinically unwell were excluded. Nikam et al used a longer 15 minute intervention period in this study, compared to 5 minutes in most previous studies.

They found a success rate of 70% in this longer 15 minute timeframe, with greater success in younger infants (0-3 months) compared to older infants (4-6 months). Success for voiding in the non-intervention group was not reported, but contamination was reported to be lower in the intervention group (27%) compared to the control clean catch group (49%).

4.7.3.6 Summary of bladder lumbar stimulation in ED studies

Results from these studies of the bladder-lumbar method in the ED setting found success rates of 27-49% for studies reporting a 5 minute success rate. This is lower than the success found in the neonatal setting, and no studies in the ED setting were randomised.

Most of these studies excluded participants with poor feeding and dehydration or they were specifically offered fluids 20-30 minutes prior to the intervention, although in practice many of the children who require urine sample collection in the ED have poor oral intake. Some of these studies also included only younger infants less than 6 months of age, who may be more likely to respond to voiding stimulation than older infants. Additionally, in most studies the intervention was performed by the research team or specifically trained staff, which limits generalisability.

Contamination was reported for some studies, but different definitions of contamination limits comparison between settings. Interestingly however, two studies suggested that the intervention reduced sample contamination.

Success was more likely in younger and smaller infants in most studies, and one study reported specific difficulties maintaining the position of heavier children.

4.7.4 Vibrating bladder stimulator device

4.7.4.1 Davies et al (2008)

In 2008 Davies et al evaluated the use of a vibrating bladder stimulator device to facilitate urine sample collection for pre-continent children in a UK ED. [127]

Adult studies had shown that vibrating bladder devices can facilitate bladder emptying for patients with neurogenic bladder secondary to neurological conditions such as multiple sclerosis. [235 242] Based on these studies, Davies et al hypothesised that a commercially available handheld battery-operated bladder stimulation device could stimulate urination in young children. The

device used was the percutaneous Queen Square bladder stimulator (Figure 9), a circular massager with a 60Hz vibrating disk, used by pressing the device on the lower abdomen 2.5cm above the pubic symphysis.

Figure 9: Queens Square vibrating bladder stimulator



Image from Dasgupta et al, British Journal of Urology 1997 (reproduced with publishers permission) [242]

This randomised non-blinded study evaluated this bladder stimulation device for pre-continent children who required a urine sample in the ED. Unlike many other voiding stimulation studies, children with poor feeding and dehydration were not excluded. 110 children were recruited and 97 included in the analysis. Urine collection and additional intervention was performed by parents in the ED. The parents of 49 children in the control advice group were "given a sheet detailing methods of stimulating urine flow by massage, tapping the abdomen and offering drinks". Those in the intervention device group were "shown how to operate the stimulator and advised to use this for 1 min out of every 5, as well as offering drinks". The primary outcome was time until urination.

The bladder stimulator device did not provide any improvement in time to void compared to the advice group. 10% of parents using the device commented on their child being upset by its use. The authors also note that the device was noisy, and some parents allocated the device chose not to use it.

Although not the primary aim of the research, this study does provide some helpful baseline data on time to void for routine clean catch sample collection. The authors found children in the study spent on average 1 hour waiting for a urine sample. 48% passed urine within 1 hour and 80% passed urine within 2 hours. Approximately 25% of children who required a urine sample left the department without a sample being obtained.

4.7.4.2 Summary of vibrating bladder stimulator device

One study of a vibrating bladder stimulator device found it did not improve the success of urine sample collection for young pre-continent children in the ED.

4.7.5 Summary of existing voiding stimulation methods

Voiding stimulation methods have the potential to improve urine sample collection for young pre-continent children who require evaluation for potential UTI. Three methods have been previously evaluated, but studies to date have not provided definitive evidence to achieve this goal.

The finger tap method studies from the 1980s were poorly described and have significant methodological limitations. The bladder-lumbar stimulation method appears promising in neonates, but requires three operators and is more challenging and less successful in older infants. Vibrating bladder stimulation devices have not proven effective in children.

Many of the studies to date have excluded participants with poor feeding or dehydration. Others have mandated feeding 20-30 minutes prior to the intervention, which may be impractical in some settings. Only two studies were randomised, and no other studies included a proper comparison group. Most but not all studies have evaluated a 5 minute intervention duration.

A recent systematic review published in January 2020 also evaluated the evidence for bladder voiding stimulation techniques used for urine sample collection in pre-continent children. [243] The systematic review did not identify any additional studies not already included in this literature review.

There is a need to develop a new voiding stimulation method which is both practical and effective, and suitable for all pre-continent children including those that may be unwell or dehydrated. There is also a need to compare intervention success to standard practice, preferably in a randomised trial to control for confounders.

Therefore the doctoral candidate conducted an initial pilot study of the previously described Quick-Wee voiding stimulation method to establish feasibility of this new method (Paper 2), with a concurrent co-authored baseline study (Appendix 11.1.6) to establish the comparison 5 minute success rate of standard clean catch practice.

4.8 PILOT STUDY: METHODS & RESULTS

This was a pilot study utilising a prospective convenience sample of participants in the ED. It measured the success of obtaining a clean catch urine sample using the Quick-Wee voiding stimulation method during a 5 minute intervention period.

The study was designed to establish the feasibility and acceptability of the novel Quick-Wee method, and provide the basis for sample size and power calculations for a subsequent larger RCT of the Quick-Wee intervention.

The main methods and results are published as a peer reviewed short report in *Emergency Medicine Journal*, and the published paper is included below:

4.8.1 Published results paper (Paper 2)

Quick-Wee: a novel non-invasive urine collection method

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ABSTRACT

Background Clean catch urine (CCU) collection in precontinent children is often time-consuming, with associated collection failure. We hypothesise that stimulating cutaneous reflexes hastens voiding for CCU.

Methods 40 children aged 1–24 months in the ED. Standard CCU was augmented with gentle suprapubic cutaneous stimulation using saline-soaked gauze (Quick-Wee method).

Results 12/40 (30%) children voided within 5 min for successful CCU. Parental and clinician satisfaction was high.

Conclusions Quick-Wee appears to be a simple method to speed CCU in young children.

INTRODUCTION

Urinary tract infections (UTIs) are common in young children, clinical signs vary and if unrecognised further complications can occur.

Collecting uncontaminated urine from precontinent children is challenging. Non-invasive methods (perineal bag, clean catch) are convenient but time-consuming, with high contamination[1] and collection failure.[2 3] Invasive methods (catheter, suprapubic aspiration) reduce contamination[1] and are potentially faster, but require expertise and cause pain and distress.

Clean catch urine (CCU) collection involves waiting to catch midstream urine if a nappy-free child voids spontaneously. CCU is commonly used and recommended by UK guidelines for young children with suspected UTI.[4] American guidelines however suggest CCU can be used for screening, but not definitive diagnosis before initiating treatment.[5]

CCU can be time-consuming, with average time waiting for CCU of 1 hour in a previously published study.[3] Based on preliminary data from a current study, median time to void is 25 min but only 12% void within 5 min.[2] Improved non-invasive collection would have major benefits, and is recommended for future research.[5] Previously investigated techniques include a vibrating bladder-stimulator in young children (not effective)[3] and bladder/lumbar stimulation in neonates (effective, but neonatal age-group only).[6 7]

Anecdotally many children void during routine perigenital cleaning before urine collection attempts. We hypothesise this stimulates newborn cutaneous voiding reflexes, triggering involuntary parasympathetic detrusor contraction via exteroceptive somatobladder mechanisms.[8] These reflexes are observed when animals stimulate voiding by licking their newborn's perigenital skin.[9]

This study trials a new pragmatic technique to elicit voiding reflexes for CCU within 5 min in young children.

METHODS

Design: Prospective feasibility study using gentle cutaneous stimulation with saline-soaked gauze (Quick-Wee method) to trigger voiding. The hospital Ethics Committee approved the study (ref.35083A).

Setting: ED, Royal Children's Hospital Melbourne.

Sample size: Convenience sample of 40 patients to assess proof of concept and feasibility, and determine sample size for a potential randomised controlled trial (RCT).

Participants: Precontinent children (aged 1–24 months) where treating clinicians required urine collection. Children were excluded if they had urogenital or neurological abnormalities affecting voiding, or required alternate urine collection methods. Demographics, comorbidities and CCU indication were recorded.

Procedure: Verbal and written study information was provided, before parents provided verbal consent. Trained clinicians performed 10 s standardised perigenital cleaning with room-temperature sterile water-soaked gauze, then additionally rubbed the suprapubic area with saline-soaked gauze held by disposable plastic forceps in continuous circular motions (see figure 1), for up to 5 min.

To determine if temperature influenced voiding success or adverse effects, for 20 children room-temperature saline-soaked gauze was used, and for 20 cold saline (2.8°C refrigeration).

Primary outcome was voiding within 5 min. Secondary outcomes were a parent or clinician successfully catching urine if children voided, and parent and clinician satisfaction (5-point Likert scale).

RESULTS

Forty patients participated in the study: no families declined participation. CCU indications included fever of unknown origin (42.5%), vomiting (17.5%), unsettled baby (17.5%), specifically suspected UTI (15%), failure to thrive (5%), other (2.5%). Four patients had minor renal abnormalities (three antenatally diagnosed hydronephrosis, one duplex kidney), one had previous UTI.

Twelve children (30%) had successful voids within 5 minutes (see table 1). Mean age of patients who voided was 3.7 months, all were <12 months, 10 <6 months of age. Urine was successfully caught in a specimen jar on all occasions. More



Figure 1 Quick-Wee method.

Table 1 Results

	Room-temperature group	Cold-temperature group	All children
Number	20	20	40
Male	12/20 (60%)	18/20 (90%)	30/40 (75%)
Age in months, mean (range)	7.5 (2–15)	5.7 (1–16)	6.6 (1–16)
Voided urine (%) (95% CI)	5/20 (25%) (9% to 49%)	7/20 (35%) (15% to 59%)	12/40 (30%) (17% to 47%)
Successful catch	5/20 (25%)	7/20 (35%)	12/40 (30%)

voids occurred using cold-soaked gauze, but 95% CIs overlapped.

Satisfaction with Quick-Wee was high. Thirty-five of 40 parents (87.5%, 95% CI 73% to 96%) and 36/40 clinicians (90%, 95% CI 76% to 97%) were satisfied or very satisfied (Likert score 4 or 5). No adverse events occurred and no respondents were unsatisfied with the intervention.

DISCUSSION

This simple method has a promising 5 min voiding rate of 30%. The yield appears higher in younger infants which may be expected given the hypothesis of stimulating newborn cutaneous voiding reflexes, which likely diminish with age.

Although comparison is limited by possible confounders, a study from the same ED found a much lower voiding rate of 12% within 5 min with standard CCU in 218 children 2–48 months of age (mean 11.4 months, median 10 months, boys 61%).[2]

A limitation of this study is the small sample size and a lack of a contemporaneous comparison group; however, our aim for this exploratory study was to demonstrate proof of concept and the feasibility of this novel method performed by a single clinician. Other reported methods to facilitate voiding in infants require three staff to perform,[6 7] and may not be practical in older or heavier infants. There may be an important age effect related to the maturity of the reflex arch which could be explored in a larger study.

Obtaining urine from precontinent children remains challenging. Expediting CCU could reduce painful invasive collection methods and improve satisfaction with CCU. With such a simple intervention, even a modest improvement would be of clinical benefit.

The Quick-Wee method of saline-soaked gauze suprapubic stimulation appears promising to speed CCU in young children. Further studies are required to evaluate its efficacy in the ED.

Acknowledgements The authors thank the families and clinical staff participating in this trial.

Contributors JK was responsible for identifying the research question. All authors contributed to the study design and development of the protocol. JK was responsible for drafting this paper and finalising the manuscript. All authors provided comments on the drafts and approved the final version.

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Competing interests None declared.

Ethics approval Royal Children's Hospital Human Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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4.8.2 Further detail of methods and results

Some additional details for the pilot study methods and results which are relevant to this doctoral thesis are included below.

The participant information sheet and case record form (CRF) are included in Appendices 11.2.1-11.2.2.

4.8.2.1 Study management, roles and responsibilities

The doctoral candidate was the lead researcher and clinician responsible for initiating, co-ordinating and implementing the study. All study co-authors advised on the study design and methodology. Dr Shidan Tosif and Dr Patrick Fitzpatrick assisted with implementation in the ED. A/Prof Ed Oakley and Dr John Cheek provided peer review of the study protocol. The doctoral candidate wrote the first and final versions of the study protocol, ethics application and manuscript, which were reviewed by all co-authors.

4.8.2.2 Intervention

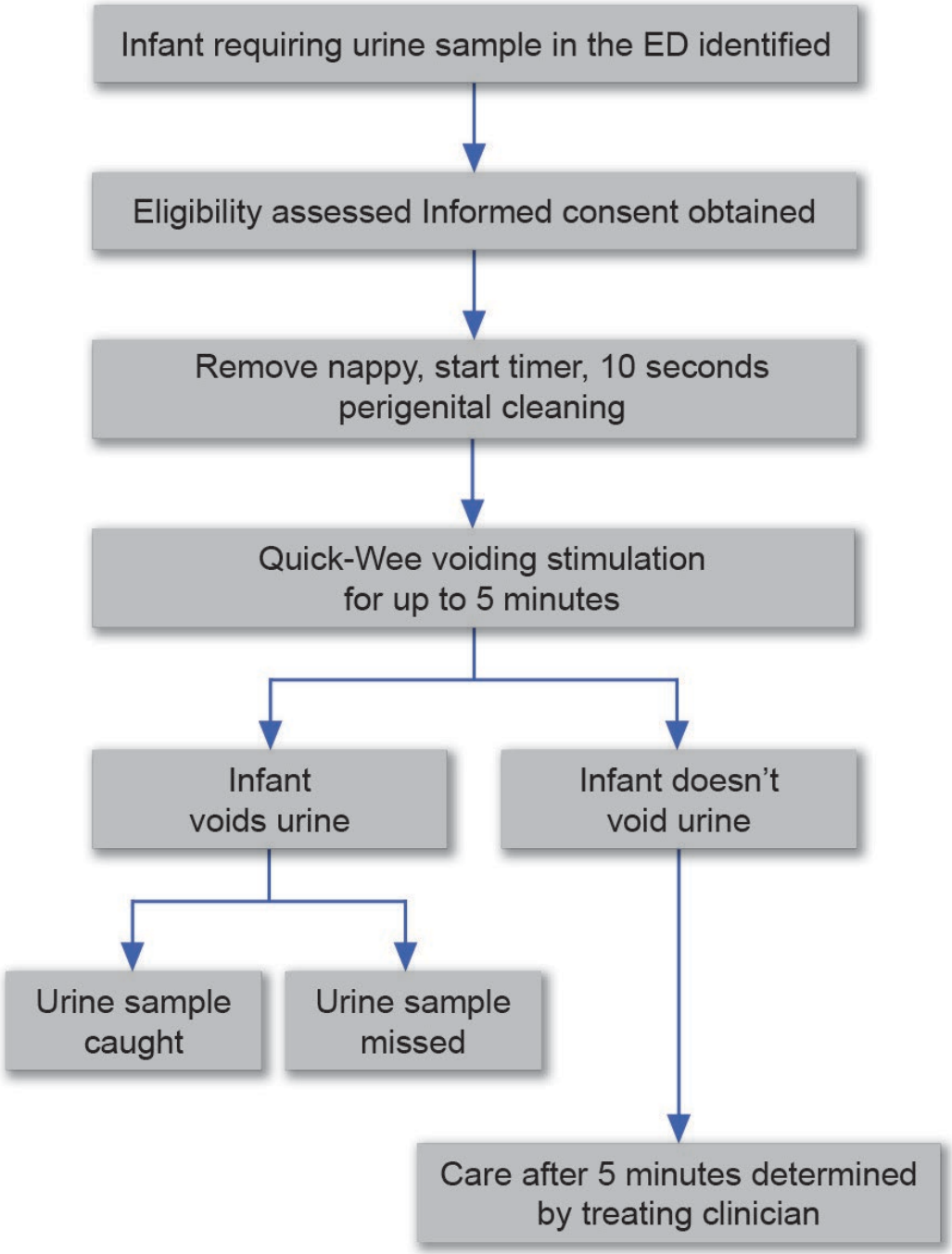
The Quick-Wee voiding stimulation method of suprapubic cutaneous stimulation with saline soaked gauze has been previously described in section 4.5.4. In this pilot study, both room temperature and cold saline were used separately for the intervention for different groups of participants.

While warm stimulation could potentially be beneficial in triggering voiding reflexes, the inadvertent use of hot stimulation has a risk of causing burns to sensitive infant skin. Therefore for safety reasons it was decided to only use cold or room-temperature stimulation in trials of the Quick-Wee method.

It has been suggested that cold thermal stimulation could cause burns to the sensitive skin of children, [127] however to our knowledge there is no evidence to validate this hypothetical concern. It was therefore appropriate to use cold fluid while monitoring closely for any adverse reactions, as well as for comparison between cold and room-temperature fluids.

Ampoules of saline were used for the intervention as they are easily available, cheap and easily refrigerated. However it is likely that any cold fluid would have a similar effect.

Figure 10: Flow of participants through the pilot study



The intervention was ceased if the child voided urine and a sample was successfully collected in a specimen jar, or after 5 minutes (Figure 10).

The research team member timed the 5 minute intervention duration using a digital timing device. If no sample was collected during the 5 minute intervention period, the treating clinician made all decisions about ongoing care, which typically was to continue with a routine clean catch collection attempt without further additional stimulation.

4.8.2.3 Ethics

Prospective ethics approval was obtained from the hospital Human Research Ethics Committee. The doctoral candidate was the principal investigator and wrote the first and final versions of the ethics application which were reviewed by the study co-authors.

The ethics application for the pilot study was submitted as a linked protocol including a prospective observational study (baseline study), which would contribute to the feasibility and sample size calculations for the proposed subsequent RCT. The section of the ethics application relating to the prospective observational study was written jointly with Dr Shidan Tosif.

4.8.2.4 Study recruitment

The doctoral candidate and 3 other clinicians recruited participants and performed the intervention: Dr Patrick Fitzpatrick, Dr Sandy Hopper and Dr Michelle Waterham.

Prior to commencing the study, the doctoral candidate conducted individual face-to-face training sessions with members of the study team who would be performing the intervention, and demonstrated the intervention using an infant mannequin, to ensure standardised implementation.

4.8.2.5 Patient population

The patient population was children aged 1-24 months.

The upper age range of 24 months was chosen to include the majority of pre-continent children but exclude continent children, as in Western society volitional bladder control is usually achieved beyond 2 years of age. [224 227]

Neonates aged <1 month were not included in the study, because local guidelines do not recommend clean catch urine collection in this age group. Catheter or SPA collection are recommended in neonates to avoid sample contamination, due to the higher risk of sepsis in neonates and potential clinical difficulties with contaminated samples.

4.8.2.6 Sample size

A sample size of 40 infants and young children was chosen for this pilot study, divided into two groups (cold or room temperature fluid interventions) to determine if the temperature of the fluid influenced the success of the intervention.

The research team felt this was a large enough sample to demonstrate proof of concept for the intervention, establish feasibility of the method in a busy clinical environment, refine the intervention and trial methods prior to the planned RCT, and reveal any unanticipated harms or adverse events cause by the intervention.

4.8.2.7 Study location

The study was conducted in the ED of the Royal Children's Hospital (RCH). The RCH is a tertiary paediatric hospital in Melbourne, Australia. The RCH ED has an annual census of approximately 90,000 patients.

4.8.2.8 Adverse event reporting

An adverse study event was defined as an undesirable medical event occurring to a participant while enrolled in the study and related to the study intervention, whether caused directly or indirectly by the intervention.

A serious adverse study event was defined as an undesirable medical event occurring to a participant while enrolled in the study and related to the study intervention, which required specific monitoring or treatment by hospital staff.

Anecdotally, transient crying often occurs with standard care for urine collection attempts such as clean catch without voiding stimulation. Therefore transient crying was not regarded as an adverse event in this study, which is consistent with previous published voiding stimulation studies. [140 234]

Adverse events if they occurred could be recorded by the treating clinician or member of the research team on the CRF.

4.8.2.9 Statistical considerations and data analysis

A/Prof Susan Donath advised on the statistical analysis plan. Statistical calculations were performed by the doctoral candidate using Microsoft Excel and Stata 14 (StataCorp, US).

Demographic and clinical background data was reported using numbers and percentages, with mean and range reported for patient age.

Success for voiding urine and urine sample collection with the Quick-Wee intervention were analysed as binary outcomes (child voids and urine sample obtained within 5 minutes: yes/no), and reported as a number, percentage and 95% confidence interval.

Parent and clinician satisfaction was reported as the percentage and 95% confidence interval of respondents who were either satisfied or very satisfied (Likert score 4 or 5) with the intervention.

Study withdrawals, protocol violations and missing data if applicable were to be noted, but excluded from analysis, although this did not actually occur in the pilot study.

4.8.2.10 Recruitment

40 participants were recruited over a 3 month time period. The patient's treating clinician (nurse or doctor) made a decision about the need to obtain a urine specimen on clinical grounds. The treating clinician then decided if clean catch was an appropriate method of urine collection for the child. These decisions about usual care were made completely independently of the research project.

No eligible participants who were approached to participate in the study declined or refused consent. There was no missing data for any participants in this pilot study.

4.8.2.11 Contamination

3 of the 12 urine samples (25%) collected during the 5 minute intervention period were found to be contaminated on subsequent evaluation of laboratory results.

4.8.3 Discussion

This pilot study demonstrated that the Quick-Wee method is safe, feasible, acceptable to clinicians and caregivers, and likely to be effective. This knowledge provided the basis for a subsequent larger and definitive RCT.

4.8.3.1 Safety of the method

No adverse events occurred during the study, indicating the intervention is safe.

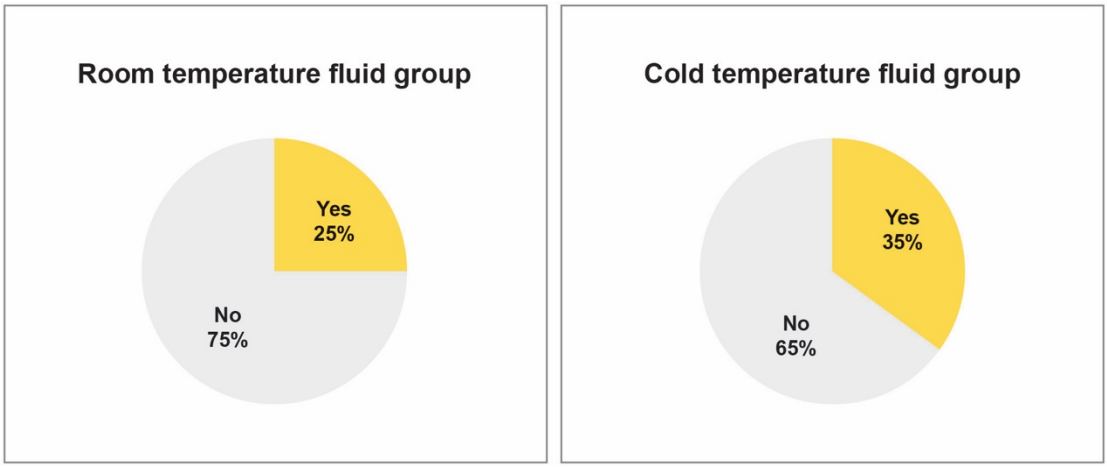
4.8.3.2 Feasibility

No problems or difficulties were recorded in the open comments section of the CRF for any participants in the study, indicating feasibility of the intervention and study methods.

4.8.3.3 Effectiveness of the method

Twelve out of forty participants (30%) voided urine within the 5 minute intervention period. In the room temperature group the success rate was 25% (5/20) and in the cold temperature group it was 35% (7/20) (Figure 11). A urine sample was successfully collected on all occasions when the child voided.

Figure 11: 5 minute voiding success using the Quick-Wee method



The promising success rate in this pilot study therefore provided a signal that the method is likely to be effective.

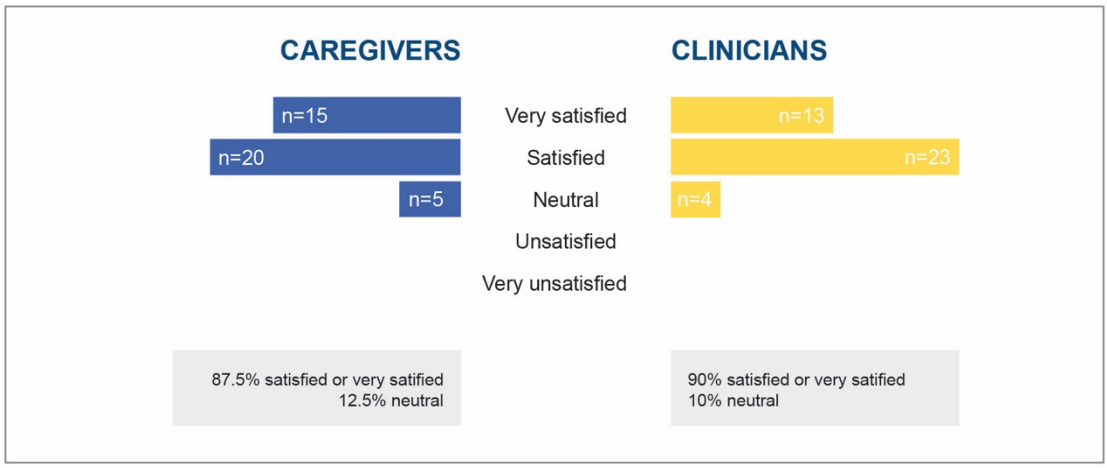
4.8.3.4 Caregiver and clinician satisfaction with the method

Satisfaction with the Quick-Wee method was high (Figure 12), as recorded using a 5-point Likert scale (5 = very satisfied, 4 = satisfied, 3 = neutral, 2 = unsatisfied, 1 = very unsatisfied).

Of the 40 caregivers, 15 (37.5%) rated the intervention as Very Satisfied, 20 (50%) as Satisfied, and 5 (12.5%) as Neutral. No caregivers rated the intervention as Unsatisfied or Very Unsatisfied.

Of the 40 clinicians, 13 (32.5%) rated the intervention as Very Satisfied, 23 (57.5%) as Satisfied, and 4 (10%) as Neutral. No clinicians rated the intervention as Unsatisfied or Very Unsatisfied.

Figure 12: Caregiver and clinician satisfaction with Quick-Wee method



4.8.3.5 Influence of age on effectiveness

The mean age of patients who voided within 5 minutes was 3.7 months, which was younger than the mean age of children of 6.6 months in the study overall.

Of the 12 children who voided, all were less than 1 year of age, and 10 were less than 6 months of age. This is consistent with the hypothesised underlying physiological mechanism being a newborn cutaneous voiding reflex, and knowledge that most newborn reflexes fade within the first 12 months of life. The higher success found in younger infants in this pilot study is also consistent with the higher success rates reported in neonates and younger infants for bladder-lumbar stimulation manoeuvres from previous and subsequent studies. [140 234 236 239 240]

Therefore a narrower age range of 1-12 months was selected for the subsequent RCT.

4.8.3.6 Influence of sex on effectiveness

Overall 30 of 40 (75%) of children in the study were male, and 10 of 12 (83%) children who voided within 5 minutes were male.

In the room temperature group, 3 of 5 children who voided within 5 minutes were male (60%).

In the cold saline group, 7 of 7 children who voided within 5 minutes were male (100%).

While there is a signal that the Quick-Wee intervention may be more effective in males than females, it was decided not to stratify recruitment for the subsequent RCT. This decision was based on the real-world application of the intervention, where urine samples are equally required from male and female children.

4.8.3.7 Influence of temperature on effectiveness

The success of the Quick-Wee method was slightly higher using cold fluid soaked gauze compared to room temperature fluid for the cutaneous stimulation. Seven of twenty (35%) children in the cold saline group passed urine within 5 minutes, compared to five of twenty (25%) children in the room-temperature saline group. However, children in the cold saline group were also younger (mean 5.7 vs 7.5 months of age) and predominantly male (90% vs 60%) compared to the room temperature group.

While the sample size for this pilot study was too small (and was not designed) to show a convincing difference between intervention temperatures given the confounders of age and sex, it does provide a signal that cold stimulation may be more effective. Therefore it was decided to use cold saline for the cutaneous stimulation in the subsequent RCT.

4.9 COMPARISON TO EXISTING CLEAN CATCH PRACTICE

While comprehensive data about the commonly used clean catch method is lacking, it has been described as time-consuming and impractical, [131] [136] and collection attempts are often unsuccessful. Contamination rates have been previously reported, [3] [137] [183] [184] [238] but the time taken and success for collection attempts has not been well described in the literature. Reliable data for time, success and contamination would allow accurate calculation of the overall diagnostic yield of clean catch attempts to actually collect an uncontaminated urine sample.

Knowledge of the specific 5 minute voiding and sample collection rate for local clean catch practice would provide a baseline to compare to the success of the Quick-Wee pilot study.

Therefore concurrently with the Quick-Wee pilot study, a baseline study of standard clean catch practice was undertaken. Dr Shidan Tosif was the lead researcher and clinician responsible for co-ordinating and implementing the trial. The doctoral candidate contributed to the study design and methodology, data collection and implementation in the ED, and reviewed and contributed to the study protocol and manuscript. The published paper is not included in this chapter because the doctoral candidate was not the first author, but is included for reference in Appendix 11.1.6.

This baseline study was specifically planned and designed to inform and enable protocol development for the subsequent Quick-Wee RCT, and so a brief synopsis of the study aims, methods, findings, and importance of findings to inform the RCT are described below. [244]

4.9.1 Aims

1. The main aim of the baseline study was to determine the time, success and outcomes of clean catch collection attempts.

2. The second aim was to determine a baseline 5 minute clean catch collection success rate, for clean catch collection attempts using standard practice.

This baseline success rate could then be compared to the intervention success rate from the concurrent pilot study. The comparison would allow estimation of the size of the treatment effect for the Quick-Wee intervention, and enable sample size and power calculations for the RCT.

3. The third aim was to determine the overall diagnostic yield of clean catch collection attempts to collect a definitive uncontaminated specimen.

Firstly, collection may be attempted but then unsuccessful. Even the most vigilant collector may miss the moment of voiding, resulting in a ‘missed catch’. Secondly, collection attempts may be abandoned as time goes on, with a decision made either to continue attempted collection at home, or to switch to an alternate collection method. Thirdly, a sample may be successfully collected but contaminated, and therefore diagnostically ambiguous.

The overall diagnostic yield is a critical consideration for clinicians when choosing the method of urine sample collection. For example, urine bags have high success rates but also high contamination. With a collection success rate of 96%,[137] and uncontaminated sample rate of 54%, [130] the overall diagnostic yield of bag collection attempts could be estimated as 52%. Demonstrating the overall diagnostic yield of clean catch would provide a very useful comparator for clinicians.

4. The fourth aim of the study was to evaluate if the time taken to collect clean catch samples influences contamination rates.

This may be due to an increased likelihood of the collector inadvertently touching and contaminating the specimen jar, or from the infant moving or defecating and contaminating the perigenital skin with subsequent contamination of the urine sample. Use of optimal collection technique would be expected to wane as time goes on with a tired parent trying to collect a urine sample from a sick child.

4.9.2 Outline of methods

4.9.2.1 Study design

The baseline study was a prospective observational study of pre-continent children in the RCH ED who required collection of a urine sample.

Children were included in the study if they were aged 2-48 months, pre-continent (not yet toilet trained) children, and their treating clinician determined that clean catch was an appropriate collection method.

Children were excluded from participation if there was a need for immediate urine sample via sterile method as determined by the treating clinician, they had a known urogenital tract abnormality, or were currently on antibiotics.

A convenience sample of children in the ED were recruited by RCH ED clinicians (nurses and doctors). Verbal consent was obtained for participation.

4.9.2.2 Sample size

The main purpose of the baseline study was to determine sample size and power calculations for the subsequent RCT. As described in the published paper, “The sample size was based on the estimated proportion of children voiding within 5 minutes of initiation of the clean catch attempt. This was regarded as the most important value to determine, as it would be the basis for future interventional studies”. [244] The 5 minute voiding rate with standard clean catch was estimated based on anecdotal clinical observations to be 10%. This required a sample size for the baseline study of approximately 200 participants.

4.9.2.3 Data analysis plan

A comparative analysis was performed for the proportion of voids within 5 minutes, and proportion of voids from first collection attempts, including duration of collection attempts, outcome of collection attempts, and sample contamination.

Collection attempts could have one of three outcomes:

1. **Successful** (urine sample collected in specimen jar)
2. **Missed** (child voids but no urine sample obtained)
3. **Stopped** (collection attempt stopped or abandoned)

Duration of collection attempts was summarised by the median and interquartile range (IQR) as the distribution of this data was skewed. Outcome of collection attempts and contamination status were summarised by percentages with 95% confidence intervals (CI). Chi-square tests were used to compare outcome proportions between groups.

4.9.2.4 Study procedures

Clean catch urine collection was performed by clinicians as per existing 2015 RCH and statewide Victorian clinical practice guidelines. [64]

Standardized collection packs were provided from designated study boxes located at the two main ED staff bases, containing sterile water for perigenital cleaning, gauze, a urine jar, digital timer, the Parent Information Sheet and data collection Case Record Forms. Data was collected on patient demographics and the clinical indication for urine sample collection.

The digital timer was started at the commencement of the collection attempt when the nappy was removed, before commencing any cleaning of the perigenital area. After initial skin cleaning (standard practice) no additional stimulation to induce voiding was performed. The timer was stopped if the child voided urine (if either a sample was successfully collected, or if there was a missed catch) or if the collection attempt was abandoned or interrupted. The time taken and outcome for all clean catch attempts, time to voiding if the child passed urine, and the clinician's plan if the initial collection attempt was unsuccessful, were recorded by the clinician. Urine culture and contamination results were subsequently obtained from the hospital laboratory database by the research team.

The study was conducted in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines for observational studies. [245]

4.9.2.5 Laboratory urine culture definition

Contamination was defined by standard laboratory procedures as any urine culture reported with 'mixed growth', if there were ≥2 colony types with colony forming units (CFU) ≥10000/mL, or ≥3 colony types with CFU ≥1000/mL, or where the predominant cultured organism was a known contaminant (e.g. non uropathogenic skin or vaginal flora organisms).

UTI was diagnosed when a single uropathogenic organism with CFU ≥100000/mL was present.

4.9.3 Outline of main results

4.9.3.1 Patient demographics and background

245 participants were initially recruited, and 28 were subsequently excluded, leaving 217 children eligible for participation (Figure 13). 86 participants were female (40%) and 131 were male (60%). Most participants were infants, with a median participant age of 10 months (IQR 6-18months).

The main indications for urine sample collection related to possible or probable UTI, being fever without focus (59%), vomiting (14%) and clinically suspected UTI (13%). Less common indications for urine sample collection included failure to thrive (3%), irritability (3%), oedema (1%), reduced oral intake (1%), jaundice (0.5%) and other/not specified (5%).

4.9.3.2 Outcomes of collection attempts

Of the 217 participants (Figure 13), some children had more than one collection attempt during their ED presentation.

- 187 had one clean catch attempt (86%)
- 28 had two clean catch attempts (13%)

- 2 had three clean catch attempts (1%)

Figure 13: Outcomes of clean catch collection attempts

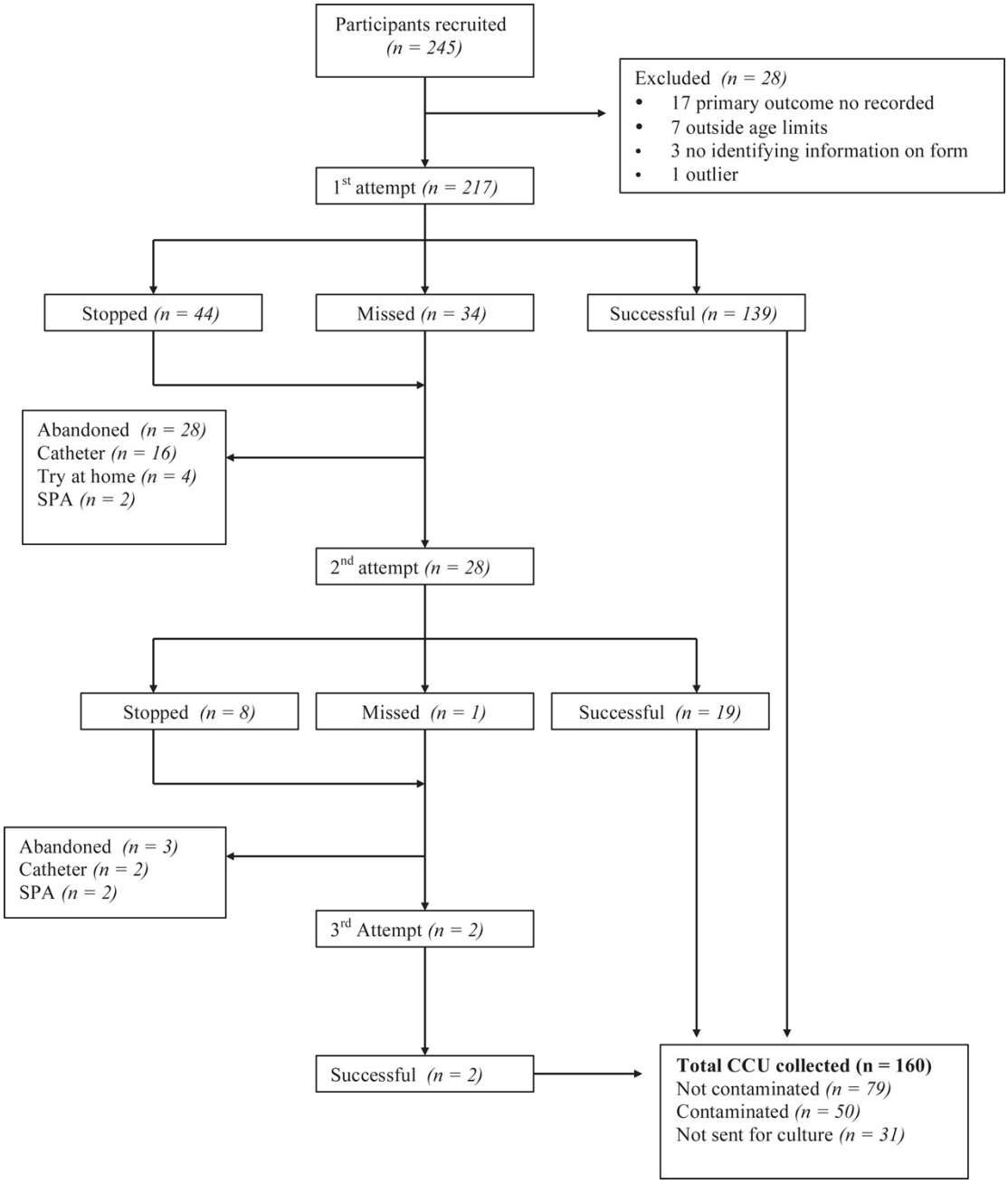


Image from Tosif et al, Journal of Paediatrics and Child Health 2017 [244] (reproduced as co-author with publishers permission)

Of 217 first collection attempts, 139 were successful (64%, CI 58-70%), 34 were missed (16%, CI 11-20%), and 44 collection attempts were stopped (20%, CI 15-26%).

Of the 217 children, 160 (74%) ultimately had a successful clean catch collection (139/217 at first attempt, 19/28 at second attempt, and 2/2 at third attempt).

4.9.3.3 Unsuccessful collection attempts

Where clean catch collection attempts are unsuccessful, the clinician must choose an alternate course of action. This may include trying again for a clean catch in the ED, potentially after optimising the child's hydration status. It may include switching to an alternate collection method, such as catheterisation, which may have a higher chance of success. It may include trying for a clean catch at home if the parents are willing to do so. Or it may include abandoning urine collection altogether, such as if the clinical picture has evolved with time and a focus of infection has become apparent, and urine collection is no longer indicated.

In this study 57 children (26%) did not have urine collected by clean catch during their ED presentation, with 22 (10%) having urine subsequently collected by an invasive method in ED, 31 (14%) having urine collection abandoned and 4 (2%) continuing attempted clean catch collection at home.

4.9.3.4 5 minute voiding

27 of 217 children voided urine within 5 minutes at the first collection attempt (12%, CI 9-18%).

For younger children <12 months of age, 16 of 114 infants voided urine within 5 minutes at the first collection attempt (14%, CI 8-22%).

4.9.3.5 Sample contamination

From the 160 urine samples obtained by clean catch in the study, 129 (81%) had urine culture performed and 31 (19%) had dipstick screening only.

Of the 129 urine samples sent for culture, 50 were contaminated (39%).

Contamination was more likely in female children compared to males (53%, CI 39-67% versus 32%, CI 20-43%, P=0.02). Contamination was also highest in the youngest age group (57% 2-6 months) compared to older age groups (36% 6-12 months, 27% 12-24 months, 33% >24 months).

4.9.3.6 UTI diagnosis

Ten children (8%) had a positive urine culture result of a single pathogen suggesting a diagnosis of UTI.

4.9.3.7 Duration of collection attempts and likelihood of success

For initial clean catch attempts, the median time spent attempting collection was 30.5 minutes (IQR 11–66).

The median time taken when the child did void urine and collection was ‘successful’ was 25 minutes (IQR 7–46.5) or ‘missed’ was 27 min (IQR 11.6–59), compared with 71 minutes (IQR 42.5–93) for clean catch attempts that were ‘stopped’ before the child voided urine.

As shown in Figure 14, the likelihood of the child voiding urine and successful sample collection plateaued after 60 minutes, plateauing further after 90 minutes.

Figure 14: Relationship of time to clean catch outcome

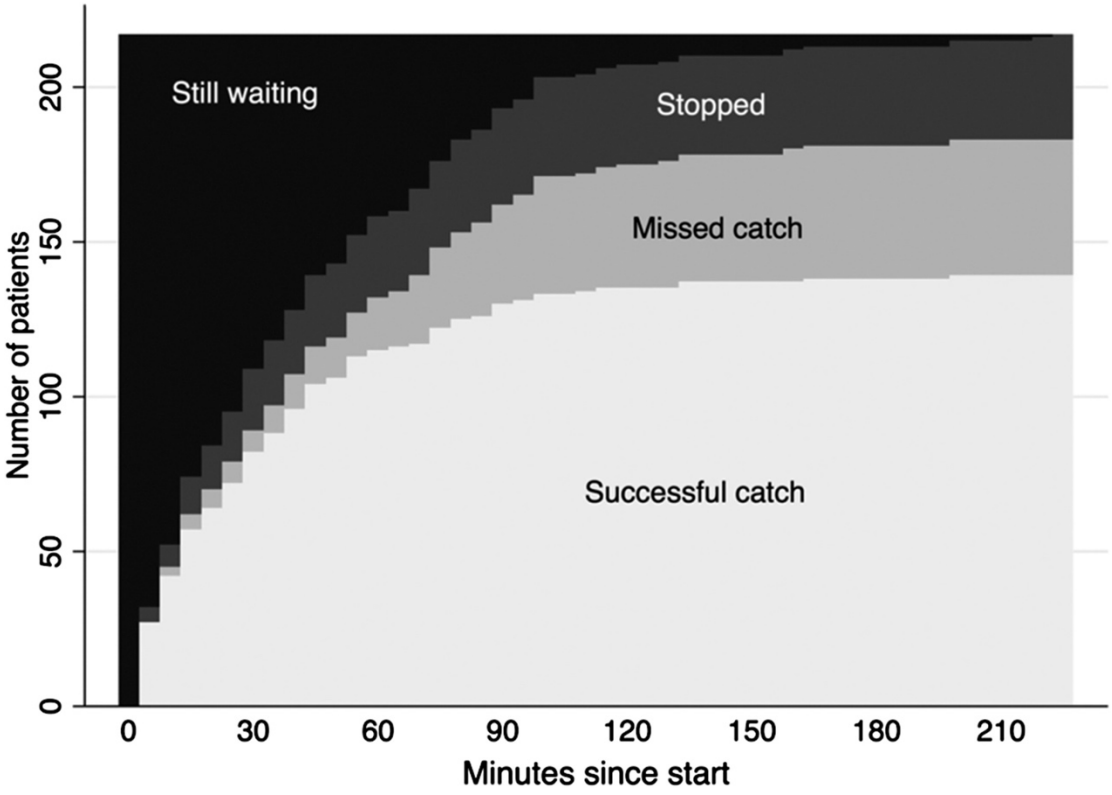


Image from Tosif et al, Journal of Paediatrics and Child Health 2017 [244] (reproduced as co-author with publishers permission)

Although it had been hypothesised that time to collection may influence contamination, in this study there was no significant difference in contamination rates by time to urine collection. When collection time was divided into 30 minute quartiles, the proportion of contaminated samples did not vary significantly overall and 95% CIs overlapped (Fig. 3 of publication in Appendix 11.1.6), although there was a trend towards increased contamination for samples collected after 90 minutes.

4.9.4 Baseline study discussion

This baseline study prospectively assessed the duration and outcome of clean catch urine collection attempts in young pre-continent children, and 5 minute voiding success rate of standard clean catch practice. The majority of

participants were infants (<12 months) having a sample collected for reasons related to potential or suspected UTI.

4.9.4.1 Clean catch attempts can be time-consuming

The first main finding of the study is that clean catch collection attempts can be time-consuming. The median duration of first collection attempts was 30.5 minutes. Three quarters of patients who voided for successful urine sample collection did so within 46 minutes. Collection success plateaued significantly after the first hour.

Time taken for clean catch has not previously been well described in the literature. In the RCT by Davies et al, [127] the average time overall for the 97 children in the study to pass urine was 63 minutes including children from both the control (advice) and intervention (vibrating bladder stimulator) arms. The time “to pass urine or leave department” in that study was 71 +/-15 minutes (mean, 95%CI) for the 48 children in the control arm.

A study by McKune et al did not provide numerical data, but provided a bar graph with collection times for the 23 successful collection attempts out of a total of 44 attempts. [131] Calculating from this graph, the median clean catch collection time was 17 minutes, and mean time was 42 minutes.

Liaw et al surveyed parents on their experiences collecting urine samples at home, [136] and while collection time was not measured, 36 of 44 parents (82%) reported that clean catch was time-consuming or impractical.

4.9.4.2 Clean catch attempts are often unsuccessful

The second main finding was that collection attempts are frequently unsuccessful. Only 139 of 217 (64%) of first collection attempts resulted in a urine sample actually being collected. Many children required multiple collection attempts, and overall 160 of 217 (74%) had a clean catch sample obtained during their ED presentation. 22 of 217 (10%) children had their urine sample subsequently collected by an invasive collection method, and 35

of 217 (16%) had collection abandoned and no urine sample collected at all in ED.

In the study by Davies et al, [127] clean catch was successful for 38 of 48 children (79%) in the control arm. Alam et al found that clean catch was successful for 168 of the 191 children (88%). [137] In the study by McKune et al, [131] 23 urine samples were obtained from 44 collection attempts (52%).

4.9.4.3 Clean catch samples are frequently contaminated

The third main finding was that clean catch samples are frequently contaminated. Contamination was more likely in females and in younger infants <6 months. Overall, 39% of samples were contaminated.

This is higher than previous studies which have reported clean catch contamination of 5-27%, [137 140 141 236] including a previous retrospective study from 2012 conducted in the same department (RCH ED) which found contamination of 26% for 202 participants. [3]

Comparing contamination rates between studies conducted in different settings may be difficult, as collection technique including pre-collection cleaning, as well as laboratory definitions of contamination, may vary.

4.9.4.4 Time to collection does not influence contamination

Time to collection did not influence contamination, which was an unexpected finding. We had hypothesised, based on anecdotal clinical observations, that accidental contact between the specimen jar and the collectors' fingers or the child's perigenital skin was more likely as time progressed. Contamination may occur when urine flushes the distal urethra, foreskin and labia on voiding. This explanation is supported by the ballooning of the prepuce and vaginal reflux of urine seen with voiding in a proportion of children (38% boys and 14.3% of girls) on micturating cystourethrograms. [26] Therefore current local practice of cleaning the perigenital skin by rinsing with water before collection may be insufficient to remove sufficient numbers of colonizing skin bacteria.

While a midstream urine sample is recommended in continent children and adults for this reason, so that incidental skin flora are washed away with the discarded first void urine, a definite midstream sample is much more difficult to achieve in a young pre-continent child.

4.9.4.5 The overall diagnostic yield of clean catch samples is low

Overall, the diagnostic yield of clean catch collection attempts in this study was low.

The proportion of successfully collected and uncontaminated urine cultures obtained overall was 79 of 217 (36%). However, some samples were only used for dipstick screening and a urine culture was not requested for all samples.

The proportion of contaminated samples in this study was 39%. Therefore the proportion of uncontaminated samples in this study was 61%.

From first collection attempts only (success 139 of 217, 64%), the overall diagnostic yield to successfully collect an uncontaminated specimen would be estimated as 39% (64% success x 61% uncontaminated).

If all urine samples collected by clean catch from any collection attempt in the ED (success 160 of 217, 74%) were sent for culture, the overall diagnostic yield would be estimated as 45% (74% success x 61% uncontaminated).

There is limited previously published data available for comparison. McKune et al found a success rate for clean catch of 52% (23 successful collections from 44 attempts), [131] with a contamination rate of 0% (none out of 23 samples). The reporting of methods from the McKune study however were limited, for example it is assumed the 44 collection attempts were for separate children but this is not stated explicitly.

Another study by Alam et al (2005) of 191 children under 3 years of age found a success rate of 82% and contamination rate of 15% for clean catch, [137]

giving an overall diagnostic yield of 70% (82% success x 85% uncontaminated).

4.9.4.6 5 minute voiding success rate

Only 12% of children in his study voided within 5 minutes.

In the study by McKune et al (1989) the specific times to void are not reported, but the bar graph provided in the paper shows that the time taken for successful urine collection was 1 minute for 1 child and 5 minutes for 4 children, out of 44 Clean Catch collection attempts. This indicates an 11% 5 minute voiding success rate overall (5 of 44 attempts).

4.9.5 Implications for practice and further research

4.9.5.1 Clinical implications

The findings of this baseline study have important clinical implications, as this study demonstrated that clean catch collection attempts are often time-consuming and unsuccessful.

Clean catch has an overall diagnostic yield of 45% in the ED (success rate 74% and uncontaminated rate 61%). This challenges the place of clean catch as the non-invasive collection method preferred by clinicians, [142] and highlights the need to improve the success and reduce the contamination of non-invasive urine sample collection.

The bladder-lumbar voiding stimulation method originally described by Herreros has been shown to improve the success of clean catch collection in neonates. [140] The Quick-Wee method has been shown to be feasible in the preceding pilot study, [246] and therefore could be an effective way to improve non-invasive sample collection in infants.

4.9.5.2 Sample size and power calculations for the Quick-Wee RCT

This data provides an important baseline 5 minute voiding rate for standard clean catch practice.

It is unlikely that any urine collection method would have a 100% 5 minute success rate. Therefore it is possible to survey clinicians to ascertain the level of treatment effect that they would consider worthwhile, that would convince them to introduce a new method into their clinical practice. This level of desired treatment effect above the baseline 5 minute voiding rate informed sample size and power calculations for the subsequent RCT.

Therefore the pilot study feasibility data, together with the baseline study 5 minute voiding data, were a foundation for the subsequent Quick-Wee RCT which is described in further detail in Chapter 5.

4.10 CHAPTER SUMMARY

The primary aim of this chapter was to describe the development of a simple voiding stimulation method for faster and more effective non-invasive urine sample collection for young pre-continent children.

Quick-Wee is a novel voiding stimulation technique that could achieve this aim. The simple intervention consists of gentle suprapubic cutaneous stimulation, using wet gauze, which triggers involuntary voiding reflexes.

Quick-Wee has several practical advantages over other voiding stimulation methods. Firstly, only a single operator is required, compared to the two or three operators required for bladder-lumbar stimulation. Secondly, the method is simple and no specific equipment is needed beyond cold fluid and gauze, which is readily available in any clinical environment. Thirdly, the method is more practical in older and heavier infants, for whom bladder-lumbar stimulation may be challenging.

The Quick-Wee pilot study of 40 infants and young children demonstrated proof of concept for the novel Quick-Wee method, with a 5 minute success rate of 35% with cold fluid and 25% with room temperature fluid stimulation. Feasibility in a busy clinical environment was established, with high clinician and caregiver satisfaction with the method, and no adverse patient outcomes.

In comparison a prospective baseline study of standard clean catch practice found only 12% voided within 5 minutes. The pilot data suggests that Quick-Wee could improve this 5 minute voiding success rate. The method could also possibly lower the rate of contamination.

This chapter has outlined the exploratory data that is a platform for the further research in this thesis. A subsequent RCT was then undertaken to definitively evaluate the new Quick-Wee method.

Chapter 5 QUICK-WEE: RANDOMISED CONTROLLED TRIAL

"The development of techniques that would permit an alternative to invasive sampling and culture would be valuable for general use."

American Academy of Pediatrics, Subcommittee on Urinary Tract Infection (2011) [15]

5.1 OVERVIEW

This chapter describes the Randomised Controlled Trial of the Quick-Wee voiding stimulation method

Sections 5.2 – 5.5 include the rationale for the research, aims, hypothesis, methods and published protocol paper, and elaborates further on the details of the trial methodology.

Section 5.6 includes the trial results and published outcomes paper.

Sections 5.7 discusses the strengths and limitations of the study, and the place of this study in the context of the broader literature.

PAPERS 3 & 4: RCT PROTOCOL & RCT RESULTS

The published RCT protocol paper and RCT results paper (Papers 3 & 4) form part of this chapter:

3. **Kaufman J**, Fitzpatrick F, Tosif T, Hopper S, Bryant P, Donath S, Babl F. The QuickWee trial: protocol for a randomised controlled trial of gentle suprapubic cutaneous stimulation to hasten non-invasive urine collection from infants. *BMJ Open* 2016;6:e011357. doi: 10.1136/bmjopen-2016-011357

4. **Kaufman J**, Tosif S, Fitzpatrick P, Hopper S, Donath S, Bryant P, Babl F. Faster clean catch urine collection from infants: the Quick-Wee randomised controlled trial. *The BMJ*, 2017;357:j1341. doi: 10.1136/bmj.j1341

5.2 RATIONALE

As described in Chapter 2, UTIs are common in young children, and many young children with fever require a urine sample to diagnose or exclude UTI as the potential source of infection. However for a number of reasons, collecting a urine sample can be challenging.

The clean catch collection method is commonly favoured, but as described in the baseline study in Chapter 3, clean catch attempts are frequently time-consuming, unsuccessful or contaminated. Only 12% of children void urine within 5 minutes. The overall diagnostic yield to successfully collect a definitive sample from all clean catch attempts is only 45%. [244]

The pilot study described in Chapter 3 demonstrated that the novel Quick-Wee voiding stimulation method is feasible to improve the success of clean catch collection. Using cold saline soaked gauze, 35% of young children voided within 5 minutes. [246] The Quick-Wee method is specifically designed to be simple, so it can be used in the community, hospital and resource-limited settings. It requires very little in the way of equipment or training, so could be easily implemented into practice.

However there was a need for a larger and more definitive trial to confirm its effectiveness, so the doctoral candidate conducted a large, rigorous RCT comparing the new Quick-Wee voiding stimulation method to the standard clean catch method.

5.3 AIMS

5.3.1.1 Primary aim

The primary aim of this RCT was:

I. To determine if the Quick-Wee method (suprapubic cutaneous stimulation with cold fluid-soaked gauze) increases the rate of voiding

urine within 5 minutes compared to standard clean catch for children aged 1-12 months.

5.3.1.2 Secondary aims

Secondary aims of this RCT were:

I. To determine if the Quick-Wee method increases the rate of successful urine sample collection within 5 minutes.
II. To determine the level of clinician satisfaction with both methods.
III. To determine the level of caregiver (parent or other carer) satisfaction with both methods.
IV. To determine if the Quick-Wee method reduces the level of contamination of urine samples collected within 5 minutes.

5.4 HYPOTHESES

The doctoral candidate hypothesised that, compared to routine clean catch urine collection (control group), the Quick-Wee method (intervention group) would:

I. Increase the rate of urine voiding within 5 minutes.
II. Increase the rate of successful urine sample collection within 5 minutes.
III. Have higher clinician satisfaction with the urine collection process.
IV. Have higher caregiver satisfaction with the urine collection process.
V. Reduce the rate of contamination of samples collected.

The doctoral candidate also hypothesised that if effective, the Quick-Wee method would also be cost-effective, by reducing the time taken and resources used for urine sample collection in the ED, which could be specifically evaluated in a subsequent health economic analysis.

5.5 METHODS

The methods for the Quick-Wee RCT are outlined in this section. This includes the published study protocol, as well as further detail and elaboration not included in the published protocol.

5.5.1 Published study protocol (Paper 3)

The study protocol was published in the journal *BMJ Open*, and is included below.

BMJ Open

The QuickWee trial: protocol for a randomised controlled trial of gentle suprapubic cutaneous stimulation to hasten non-invasive urine collection from infants

Jonathan Kaufman,[1,2,3] Patrick Fitzpatrick,[1,2] Shidan Tosif,[2,3,4] Sandy M Hopper,[1,2] Penelope A Bryant,[2,3,4] Susan M Donath,[2,5] Franz E Babl[1,2,3]

To cite: Kaufman J, Fitzpatrick P, Tosif S, *et al*. The QuickWee trial: protocol for a randomised controlled trial of gentle suprapubic cutaneous stimulation to hasten non-invasive urine collection from infants. *BMJ Open* 2016;**6**:e011357. doi:10.1136/bmjopen-2016-011357

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-011357).

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ABSTRACT

Introduction: Urinary tract infections (UTIs) are common in young children. Urine sample collection is required to diagnose or exclude UTI; however, current collection methods for pre-continent children all have limitations and guidelines vary. Clean catch urine (CCU) collection is a common and favoured non-invasive collection method, despite its high contamination rates and time-consuming nature. This study aims to establish whether gentle suprapubic cutaneous stimulation with cold fluid-soaked gauze can improve the rate of voiding for CCU within 5 min in young pre-continent children.

Methods and analysis: This study is a randomised controlled trial of 354 infants (aged 1–12 months) who require urine sample collection, conducted in a single emergency department in a tertiary paediatric hospital in Melbourne, Australia. After standard urogenital cleaning, patients will be randomised to either a novel technique of suprapubic cutaneous stimulation using cold saline-soaked gauze in circular motions or no stimulation. The study period is 5 min, after which care is determined by the treating clinician if a urine sample has not been collected. Primary outcome: whether the child voids within 5 min (yes/no). Secondary outcomes: parental and clinician satisfaction with the method, success in catching a urine sample if the child voids, and sample contamination rates. This trial will allow the definitive assessment of this novel technique, gentle suprapubic cutaneous stimulation with cold saline-soaked gauze, and its utility to hasten non-invasive urine collection in infants.

Ethics and dissemination: The study has hospital ethics approval and is registered with the Australian New Zealand Clinical Trials Registry—ACTRN12615000754549. The results of the study will be published in a peer-reviewed journal.

Trial registration number: ACTRN12615000754549; Pre-results.

Strengths and limitations of this study

- Simple, gentle, easily replicable, non-invasive technique for urine collection in young children.
- Randomised controlled trial informed by prospective baseline and pilot feasibility studies.
- Pragmatic technique and trial methodology which reflect the busy clinical environment.
- Clinicians and parents cannot be blinded to the intervention.

INTRODUCTION

Urinary tract infections (UTIs) in young children are common affecting 5–7% of febrile children under 2 years of age,[1 2] but the clinical signs of UTI can be non-specific. Urine collection is required for diagnosis of clinically suspected UTI or to determine the potential source of fever in the absence of a clear clinical focus. Limitations and ongoing debate exist with current invasive and non-invasive methods of obtaining urine samples from young pre-continent children.[3 4]

The decision on the method of urine sampling balances invasiveness (and hence pain and distress), reliability, speed and contamination rates. Clean catch urine (CCU) is often favoured for being non-invasive and requiring less technical expertise, in hospital and community-based settings,[5] and has lower contamination rates than other non-invasive methods such as urine collection bags.[6] Suprapubic aspiration and catheter specimens have lower contamination rates than CCU; however, these methods involve pain and distress for the child and require technical expertise and equipment.

Guidelines from the UK (National Institute for Health and Care Excellence),[7] USA (American Academy of Pediatrics)[8] and our local Royal Children's Hospital[9] have differing recommendations for the use of CCU for urine collection from febrile infants with

suspected UTI. Contamination rates in CCU are high and variable, reported as between 7.8% and 35%.[6 10–12]

CCU also ties up valuable resources in clinical settings due to its time-consuming nature, and parents report that obtaining a CCU is time consuming and messy.[13] This may result in increased urine contamination rates due to difficulty preventing accidental contamination of the genital area or collection jar, or CCU being abandoned by the parent or clinician. One previous study found that 58% of children waited longer than 1 hour to pass urine with CCU, with a mean time of 71 min to either pass urine or leave the department without a sample.[14]

We conducted an initial prospective baseline study to determine success in obtaining CCU with current practice, in pre-continent children aged 1–48 months. A timer was used to measure time to void after standard urogenital cleaning (without any additional stimulation). In preliminary results from the first 113 children, 13 children (11.5%) voided within 5 min.[12] Of the 57 patients who were aged <12 months, 12 patients (21%) voided within 5 min.

Previous studies have examined novel methods to obtain more rapid CCU in pre-continent children. These include vibrating bladder stimulator in infants and toddlers (not effective)[14] and lumbar/sacral stimulation in neonates (effective but limited age group).[15 16] An effective method to expedite CCU would reduce time to diagnosis, reduce the need for clinicians to instigate painful invasive urine collection methods, reduce urine culture contamination rates and likely improve parent and clinician satisfaction with the CCU method.

In animals such as rats, the mother stimulates bladder emptying by licking the perigenital skin of her newborn pups, triggering the perigenital-bladder reflex.[17] Animal model studies have also shown that mechanical and electrical perigenital skin stimulations can excite perigenital-to-bladder spinal reflexes and stimulate bladder contractions in cats with chronic spinal cord injury.[18]

In humans, suprapubic stimulation is proposed to trigger parasympathetic detrusor contraction via the exteroceptive somato-bladder reflex mechanism.[19] We hypothesise that a simple intervention of gentle suprapubic stimulation using cold fluid-soaked gauze may hasten bladder voiding, by triggering cutaneous reflexes which are present at birth and suppressed later in development.

We conducted a pilot feasibility study to test if additional suprapubic cutaneous stimulation with saline-soaked gauze was a feasible and acceptable intervention, and if this method may help to obtain CCU within 5 min in children aged 1–24 months in the paediatric emergency department (ED).[20] This was tested on 20 children using cold saline (7/20 successful, 35%) and 20 children using room temperature saline (5/20 successful, 25%). Most successful voids were from infants aged 1–12 months (12/12, 100%), so we chose 1–12 months as the participant age group for the definitive trial. CCU is not a recommended method of urine collection in neonates (<1 month) for investigation of UTI in our institution.

Our primary objective is to examine whether a simple and easily followed technique (additional suprapubic cutaneous stimulation with cold fluid-soaked gauze) increases the rate of voiding within 5 min in pre-continent children, compared to using standard urogenital cleaning alone. Secondary objectives are to study whether this method can reduce the number of urine voids that are 'missed catches', and reduce the need to use invasive urine sampling techniques in some circumstances.

METHODS AND ANALYSIS

Study aims

To determine if suprapubic cutaneous stimulation with cold fluid-soaked gauze increases the rate of urine voiding within 5 min in children aged 1–12 months in the paediatric ED, where a urine sample is required and the clinician has determined that CCU is an appropriate method of collection.

Study design and setting

A prospective randomised controlled trial (RCT) will be undertaken to compare the rate of urine voiding within 5 min using standard urogenital cleaning and CCU alone, compared with standard urogenital cleaning and CCU with additional suprapubic cutaneous stimulation with cold saline-soaked gauze.

The population to be studied is children aged 1–12 months in a single paediatric ED at the Royal Children's Hospital, Melbourne, Australia.

Eligibility criteria

Eligibility criteria for the study are listed in box 1.

Interventions

Study procedures are as follows (figure 1).

Box 1 Eligibility criteria

Inclusion criteria—all of the following:
- Aged 1 month (28 days of age) to 12 months (365 days of age), corrected for prematurity if <36 weeks gestation,
- Not able to void urine on request (pre-continent),
- Appropriate for and require clean catch urine sample collection, as determined by the treating clinician.

Exclusion criteria—any of the following:
- Children <1 month of age (<28 days of age),
- Children >12 months of age (>365 days of age),
- Need for immediate urine sample via sterile method as determined by treating clinician,
- Anatomical or neurological abnormality affecting voiding or sensation.

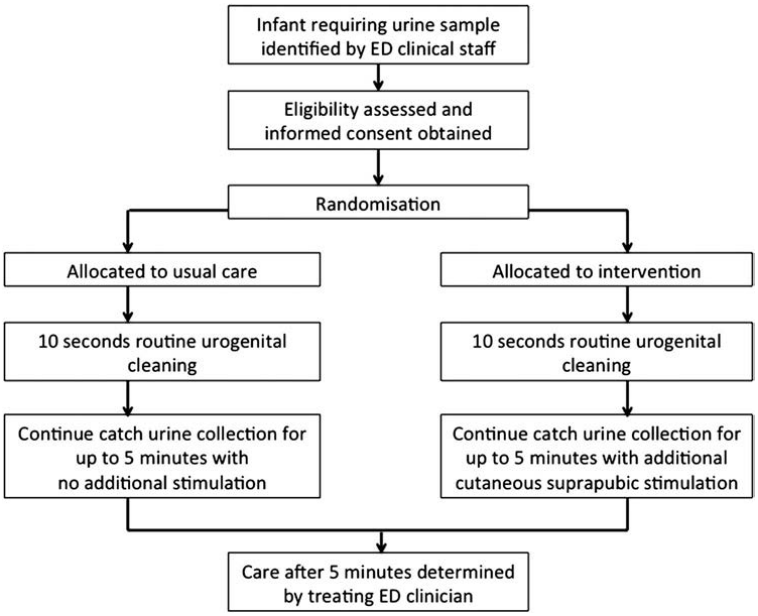


Figure 1 Study flow chart in the ED. ED, emergency department.

The clinician provides a parent information handout, verbally explains the procedure and obtains verbal consent from parents. The child is offered a bottle/breast feed prior to attempted CCU if appropriate (routine practice).

Nursing or medical staff prepare the child for attempted CCU, open the opaque randomisation envelope, remove the nappy and start the timer. A parent, carer or staff member prepares to catch a urine sample if the child voids, and the genital orifice is cleaned for 10 s (standard practice). If randomised to the usual care arm, the parent, carer or staff member waits for the child to void spontaneously, until CCU is obtained or the timer reaches 5 min. If randomised to the intervention arm, the staff member (or parent/carer with supervision) additionally rubs the suprapubic area of child with cold saline-soaked gauze held by disposable plastic forceps in a circular pattern, until CCU is obtained or the timer reaches 5 min (see figure 2).



Figure 2 QuickWee method of suprapubic cutaneous stimulation with saline-soaked gauze.

The timer is stopped if the child voids and CCU obtained and time to void recorded. Alternatively, a missed catch, failure to void at 5 min or reason for abandoning procedure is recorded as well as parent and clinician satisfaction with the method. Children who have been randomised and void during the 10 s cleaning phase will be included in the intention-to-treat analysis.

Standard urogenital cleaning for both groups will be performed using a designated standard cleaning pack with room temperature fluid for cleaning.

Additional suprapubic cutaneous stimulation will be performed using a designated pack containing disposable plastic forceps and gauze, and study-labelled cold fluid, 10 mL of 0.9% saline ampoules. The cold fluid will be stored in a designated study refrigerator with a temperature of 2.8°C (checked monthly to ensure temperature range ±1°C). Clinicians will be advised to start using the cold fluid within 2 min after taken out from the refrigerator to ensure that it remains as close as possible to the designated temperature.

When CCU is not obtained within the 5 min trial period, the clinician will make the decision on the ongoing method of urine collection (continue CCU, catheter, SPA, abandon urine collection).

Outcomes

The primary outcome measure is voiding of urine within 5 min (binary yes/no outcome).

Secondary outcome measures will be (1) parental and clinician satisfaction with the urine collection technique in each group (satisfaction rating scale 1–5: very satisfied, satisfied, neutral, unsatisfied, very unsatisfied); (2) if the child voids, whether a urine sample is successfully caught in the specimen jar or if the void is missed (binary yes/no outcome: CCU caught if child voids); and (3) contamination rate of CCU samples obtained within 5 min (binary yes/no outcome: urine culture contamination as per hospital laboratory definition).

Sample size

A sample size of 354 patients (177 in each group) will be included in the study.

In preliminary data from the preceding baseline study measuring time to void for children requiring CCU using standard urogenital cleaning alone, 12(21%) of 57 patients aged 1–12 months voided within 5 min. We surveyed a panel of 20 expert clinicians (Paediatric Emergency Medicine Physicians and Paediatricians at consultant level) who reported an increase in success rate of ~15% would suggest that this technique should be incorporated into their clinical practice. Data from the pilot feasibility study suggest that this is a reasonable estimate of the likely treatment effect.

With a sample size of 322 patients (161 in each group), the study would have 80% power to detect a difference of 21% (non-intervention arm) vs 35% (intervention arm) success rate of infants voiding within 5 min. Power and sample size calculations were completed using Stata (Statacorp 2015, Texas, USA) using an estimated total sample size for a two-sample proportions test (Pearson's χ^2 test).

An additional 10% of patients (16 in each group) will be recruited in the sample size to account for a small percentage of loss to follow-up of primary outcome results.

Recruitment

ED nursing and medical staff will be trained to recruit patients and implement the intervention with face-to-face education sessions and written instructions available in the ED. They will identify potentially suitable patients requiring urine sample collection and make a decision about the appropriate method of urine sample collection on clinical grounds (independent of this research project), at the point of triage or during clinical assessment. Patients that clinical staff consider suitable for inclusion in the study will be recruited consecutively. The parent/carer will be provided with a verbal explanation and written study information sheet, and verbal consent will be obtained to participate in the study. Recruitment began in 2015, and it is anticipated that recruitment will be completed within 12 months.

Allocation

Study participants will be randomly assigned, in a 1:1 ratio, to the intervention (additional suprapubic cutaneous stimulation with cold saline-soaked gauze) or standard care. A statistician not directly involved in the analysis of the study results prepared the randomisation schedule using random permuted blocks with at least three different block sizes to ensure concealment of allocation.

ED medical and nursing staff will enrol participants. A paper-based system, using opaque envelopes containing the allocation, will be used to assign the intervention in the ED. The allocation envelopes will be within sealed individual study packs contained in a locked study box, from which packs can only be taken sequentially. Owing to the obvious nature of the intervention, participants, clinicians and the research team analysing the data will not be blinded after randomisation and assignment to intervention.

Data collection methods

The data will be recorded by ED clinicians on paper-based case record forms (CRF), and then entered by the research team using the REDcap (Research Electronic Data Capture) electronic database hosted at the Murdoch Childrens Research Institute on the research computer server with the following parameters.

Demographic and patient data to be recorded include age and sex of patient, relevant medical comorbidities, previous UTI, known anatomical or neurological abnormality affecting voiding or sensation, reason for presentation based on triage code and clinical indication for urine collection as recorded by clinician, and reasons for exclusions and refusals.

Clinical data to be recorded include whether the child voided within 5 min and time taken to void, successful catch of urine sample (child voids and urine sample obtained), person performing standard cleaning and/or suprapubic stimulation technique (parent, doctor, nurse), person catching urine (parent, doctor, nurse), whether CCU was abandoned before 5 min and reason for abandoning procedure, and parental and clinician satisfaction with the urine collection technique.

Clinical data to be collected subsequently (by linking with laboratory data from hospital records) include whether a urine sample is collected after the 5 min study period in the ED, positive and contaminated urine culture results, admission to hospital and initiation of antibiotic therapy.

Data management and access to data

Any paper study records will be kept in locked storage cabinets. All electronic participant study records will be stored in the password-protected computer study database, accessible to the researchers only.

All study participants will be assigned a unique study number (Participant ID) for the study so that the stored data have identifiers removed but are re-identifiable.

All data entered into the study database will be checked by two members of the research team.

In accordance with state guidelines, all health information will be kept until participants reach 25 years of age, as per the Health Records Act 2001 (Vic).

Statistical methods

Data analysis for the study will be performed by statisticians at the Clinical Epidemiology and Biostatistics Unit at the Murdoch Childrens Research Institute. Statistical analysis will follow standard methods for RCTs.

The primary analysis will be performed by intention-to-treat including all randomised participants where primary outcome data are available, consistent with the CONSORT guidelines for intention-to-treat analysis.[21 22]

The primary outcome measure is a binary yes/no outcome of voiding urine within 5 min. We will report the absolute difference between the two groups for the percentage of successful CCU, together with the 95% CI for the difference of percentages, and calculate p values using a χ^2 test. A p value of <0.05 will be considered significant.

Secondary outcome measures are parental and clinician satisfaction with the urine collection technique in each group, whether there is a successful CCU caught in each group and contamination rate of CCU samples in each group.

For each secondary outcome, we will describe the rates of successful CCU and contamination for each group with percentages and 95% CIs. The appropriate difference between groups will be estimated (difference of proportions for categorical outcomes, difference of means for continuous outcomes), together with the 95% CI for the difference. The p values will be estimated using χ^2 test for categorical variables and t-test or Wilcoxon's rank-sum tests for continuous variables.

In addition to the unadjusted analysis, all treatment comparisons for primary and secondary outcomes will also be presented adjusted for age and sex to account for any chance imbalance between the treatment groups with respect to these potentially confounding factors using linear and logistic regression models for continuous and binary outcomes, respectively.

Data monitoring and auditing

No interim analysis will be undertaken: recruitment will continue until enrolment is completed. A data monitoring committee is not required for this low-risk study.

Harms

There are no foreseeable additional risks to patients or their families by participating in this study.

Should any adverse events occur, they will be recorded on the CRF and intervention can be discontinued by the treating clinician. Minor temporary discomfort to the child can be caused by cold saline cutaneous stimulation. Crying and mild distress commonly occur with routine CCU and will not be regarded as an adverse event, consistent with previous studies.[14–16]

Outlook and significance

This single-centre randomised trial will allow the definitive assessment of the utility of this novel technique to hasten non-invasive urine collection in infants. If there is a clinically significant increase in voiding success within 5 min, this low-cost simple method could be adopted widely to hasten urine collection and reduce wait times in acute care settings, and potentially reduce specimen contamination rates.

Limitations

As this is a non-blinded trial, there is the potential for the investigator to unintentionally introduce measurement or reporting bias. Owing to the nature of the intervention, it is not possible in this trial to blind the treating clinicians or study investigators.

Current status

Study enrolment has started, and recruitment and data analysis are expected to be completed by December 2016.

DISSEMINATION

Protocol amendments

Protocol amendments will be updated and freely available on the Australian New Zealand Clinical Trials Registry website.

Consent or assent

Parents will be given a parent/guardian information sheet (PGIS). Participation in the study will be discussed with the clinician and/or researcher. This will happen in the ED. The study investigators and research officer may be involved as clinicians in the clinical care of the patient.

Parents/participants will be assured that if they do not wish to participate, this will not affect their care. This is also stated in the PGIS. Verbal consent obtained from the parent/guardian (prior to undertaking sample collection) will be documented by nursing and medical staff. Refusal of consent will be recorded.

Confidentiality

Confidentiality will be ensured by storing data in a password-protected database for which only the research team will have the password, and paper-based record forms will be stored in a locked cupboard.

Any patient data published will not allow personal identification: only group data will be published.

Dissemination policy

Results will be published in a peer-reviewed publication and thesis chapter.

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Contributors JK was responsible for identifying the research question, drafting this paper and finalising the manuscript. All authors contributed to the study design and development of the protocol, provided comments on the drafts, and have read and approved the final version.

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Competing interests None declared.

Ethics approval The trial has full ethics approval from the Royal Children's Hospital Human Research Ethics Committee, HREC reference number 35083A.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Results will be published in a peer-reviewed publication and thesis chapter.

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5.5.2 Reporting guidelines: SPIRIT

The doctoral candidate followed the relevant international reporting guideline statements when designing the study protocol and writing the protocol paper for the Quick-Wee RCT.

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement provides internationally recognised guidance and evidence-based recommendations for the minimum content required in the protocol for a clinical trial. [247] It includes a checklist of the 33 recommended items to address in a clinical trial protocol, which was submitted with the study manuscript at the time of publication.

5.5.3 Administrative information

5.5.3.1 Study registration

The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR12615000754549). A copy of the trial registration is available in Appendix 11.3.1.

5.5.3.2 Protocol versions

Only one modification was made to the study protocol after trial commencement on August 10th 2015, which was to amend one exclusion criteria on 14th October 2015. The exclusion criteria was expanded from:

“Anatomical or neurological abnormality affecting voiding”

to

“Anatomical or neurological abnormality affecting voiding or sensation”

The reason for this amendment was that abnormal sensation could affect the intervention of cutaneous stimulation to the suprapubic area.

The amendment was immediately included in study materials used in the ED, and in the study protocol used by the research team. The amendment was included as a protocol update on the ANZCTR website for the trial registration.

5.5.3.3 Funding

The Quick-Wee RCT was funded by a research project grant (AUD $26,266) from the Shepherd Foundation (see Appendix 11.3.2). The Shepherd Foundation is a Victorian medical research philanthropic foundation supporting primary care prevention research.

The doctoral candidate wrote the first and final versions of the grant application which was approved by all members of the research team. The doctoral candidate and A/Prof Babl were the named Chief Investigators for the grant application. After the application was short-listed, the doctoral candidate was interviewed by the Foundation, accompanied by A/Prof Babl. The research grant was awarded on 2nd December 2015.

The Shepherd Foundation was entirely independent of the trial and did not in any way influence or contribute to the design, implementation or dissemination of the study.

5.5.3.4 In-kind support

Statisticians and clinician-researchers from the Murdoch Children's Research Institute (MCRI) and the Melbourne Children's Trial Centre assisted with advice regarding the study design, data management, and analysis and interpretation of data for this study.

The study database used the REDCap (Research Electronic Data Capture) secure web application, provided and hosted by MCRI. Ms Kaya Gardiner and Dr Luke Stevens provided advice on designing the REDCap database.

Nursing and medical clinical staff in the RCH ED recruited trial participants.

5.5.3.5 Study roles and responsibilities

The doctoral candidate was the lead researcher and clinician responsible for designing, co-ordinating and implementing the trial.

All study co-authors advised on the study design and methodology.

A/Prof Ed Oakley and Dr John Cheek provided peer review of the study protocol.

The doctoral candidate and Dr Patrick Fitzpatrick designed and constructed the designated study box and promotional materials for use in the ED, and were responsible for study promotion in the ED.

The doctoral candidate, assisted by Dr Fitzpatrick, Dr Shidan Tosif and research nurse Ms Jess Adams prepared the individual participant study packs for use in the ED.

A/Prof Susan Donath advised on statistical methods. A statistician from the MCRI who was not involved in the study prepared the randomisation schedule. The doctoral candidate performed all statistical analyses for the results paper, with guidance and supervision from A/Prof Donath and Ms Francesca Orsini.

Data entry into the REDCap study database was performed by the doctoral candidate and Dr Fitzpatrick, assisted by Dr Sandy Hopper, with additional part-time research nurse support from Ms Jess Adams, Ms Ashleigh Logan and Ms Nicole Stromiloff.

Data checking and cleaning was performed by the doctoral candidate and Dr Fitzpatrick.

A/Prof Penelope Bryant produced the line diagram of the Quick-Wee method for use in the protocol manuscript. Mr Bill Reid from the RCH Creative Studio produced the medical illustration of the Quick-Wee method for use in the results paper.

The doctoral candidate wrote the first and final versions of the study protocol, ethics application, protocol manuscript and results manuscript, which were reviewed by all study co-authors.

5.5.4 Study design

This was a superiority study, designed to determine if the Quick-Wee method was superior to usual practice with regard to the primary and secondary trial outcomes.

5.5.4.1 Study promotion

The doctoral candidate co-ordinated study promotion in the ED, and conducted over 30 face-to-face study education sessions for ED medical and nursing staff. Dr Fitzpatrick conducted a further 10 sessions.

Study flyers advertising the study aims and recruitment procedures were displayed in prominent locations in the ED. The study was also advertised at regular intervals in the internal ED bulletin and electronic newsletter.

The doctoral candidate also conducted regular informal study promotion, including a daily “walk around” the ED with a large jar of lemon sherbets as a means of initiating informal chats with clinicians about the study. Approximately 2000 lemon sherbets were distributed.

5.5.4.2 Estimation of treatment effect

An estimation of the likely treatment effect for the planned RCT was completed using preliminary data from the preceding baseline study, and a survey of expert clinicians. This was performed prior to the completion of the baseline and pilot studies, to allow the doctoral candidate to ascertain the feasibility of conducting a randomised trial, conduct sample size calculations, and facilitate timely preparation of the RCT protocol and ethics application.

From the first 100 patients recruited in the baseline study, 57 were aged 1-12 months. Of these 57 infants, 12 (21%) voided urine within 5 minutes.

20 expert clinicians were then surveyed to establish a meaningful level of treatment effect, using a visual analogue scale to measure responses. 10 senior consultant paediatricians and 10 senior consultant paediatric emergency physicians were surveyed. Clinicians were asked about the Quick-Wee voiding stimulation intervention, compared to the baseline success rate of routine clean catch:

"If this technique was successful in triggering voiding in infants in <5 minutes, allowing for expedient clean catch collection, what success rate would get you to consider trying/suggesting it for suitable patients?"

The mean of panel responses was that with a 15% increase in success rate, clinicians would be likely to incorporate the method into their clinical practice.

As reported in Chapter 3, in the preceding pilot study, 35% of children in the cold-saline arm voided urine within 5 minutes. Sample size calculations for the RCT were therefore based on an estimated treatment effect of 21% (control) vs 35% (intervention).

Ultimately in the baseline study, 16 of 114 infants <12 months of age voided urine within 5 minutes at the first collection attempt (14%, CI 8-22%). Therefore while 21% was potentially an overestimate of the control success rate, it was a plausible estimate to use for the sample size calculation, and the RCT protocol was not modified.

5.5.4.3 Power and sample size

Power and sample size calculations were completed by the doctoral candidate and A/Prof Donath, using the Stata statistical software package version 14 (StataCorp 2015, Texas, USA). The calculations were performed to determine how many participants would be needed to demonstrate the estimated difference between groups, and determine how many participants were required to avoid a Type 1 error (reject the null hypothesis incorrectly when it is true and there is no difference between the two groups, and report a difference between the two groups) and Type 2 error (accept the null

hypothesis incorrectly when it is false and there is a difference between the two groups, and report no difference between two groups). [248]

A pα (likelihood of making a Type 1 error, reject null hypothesis incorrectly) of 0.05 was chosen by convention. This pα, or significance level, equates to the chances of finding a difference between groups (when there is no difference) on less than 5% of occasions. [248]

A pβ (likelihood of making a Type 2 error, accept null hypothesis when it is false) of 0.8 was chosen by consensus amongst the study authors. The pβ, or power of the study, is the likelihood of detecting the pre-determined difference between groups when the difference truly exists, for a given pα value and sample size of N. [248] This pβ equates to finding a difference between groups when one exists on 80% of occasions.

Sample size calculations were then completed using an estimated total sample size for a two-proportions test (Pearson's $\chi 2$ test). 322 patients (161 in each group) would be required to detect a difference between groups of 21% (control) vs 35% (intervention).

It was anticipated that a small number of patients may be recruited but not complete the intervention, or not have a primary outcome recorded, for practical reasons in a busy ED. Therefore an additional 10% of patients were included in the sample (16 in each group) to account for this potential loss to follow-up until the primary outcome endpoint for some participants.

The total sample size for the RCT was therefore 354 participants (177 in each group).

5.5.4.4 Recruitment

Participant recruitment was performed by nursing and medical clinical staff in the ED, after departmental training conducted by the doctoral candidate.

All ED clinicians were invited to recruit participants for the study. ED clinicians then identified infants suitable for inclusion in the study, and assessed inclusion and exclusion criteria. Decisions about the appropriate method of urine sample collection for potential participants, and whether infants were suitable for inclusion, were made by their treating clinician, free from any influence from the research team.

Suitable participants were recruited consecutively.

No financial incentive was provided to clinicians to recruit participants. ED clinicians who recruited study participants and completed the required data entry were offered a coffee voucher to acknowledge and thank them for their assistance.

5.5.4.5 Study interventions

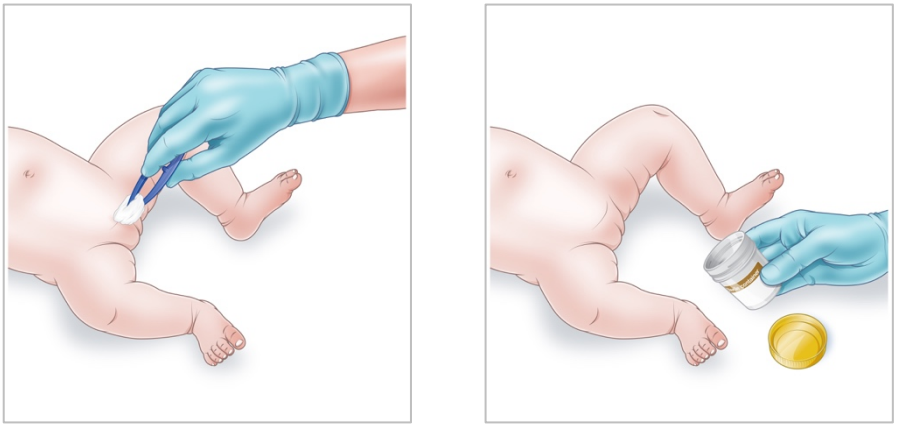
In this RCT the treatment intervention and control intervention were performed by the treating nursing or medical ED clinician.

A single page handout with explanatory photos and concise written prompts regarding the intervention were included in each individual participant study pack, which could be easily used by the clinician while delivering the intervention at the bedside (see Appendix 11.3.4).

If randomised to the control arm (usual care: standard clean catch with no additional stimulation, Figure 15), after routine cleaning the parent/carer or staff member waits for the child to void spontaneously, until a urine sample is obtained or the timer reached 5 minutes.

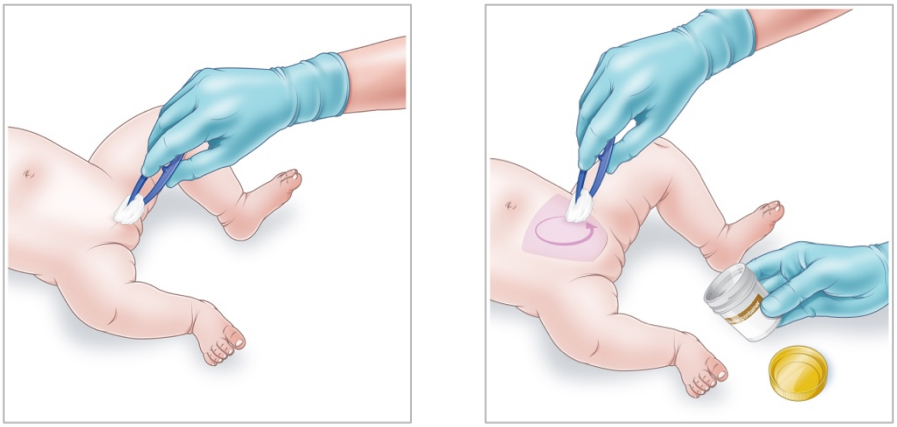
If randomised to the intervention arm (Quick-Wee method, Figure 16), the staff member (or parent/carer-giver with supervision) additionally rubbed the suprapubic area of child with cold saline-soaked gauze held by disposable plastic forceps in a circular pattern.

Figure 15: Routine cleaning and standard clean catch (control group)



Images by the doctoral candidate and Mr Bill Reid

Figure 16: Routine cleaning and Quick-Wee method (intervention group)



Images by the doctoral candidate and Mr Bill Reid

5.5.4.6 Study equipment

The process for clinicians to collect the required study equipment was a simple 3-step process (Figures 17-19):

1. Take individual participant study pack from the designated study box
2. Take timer from the study box
3. Take cold fluid study ampoules from the designated study fridge

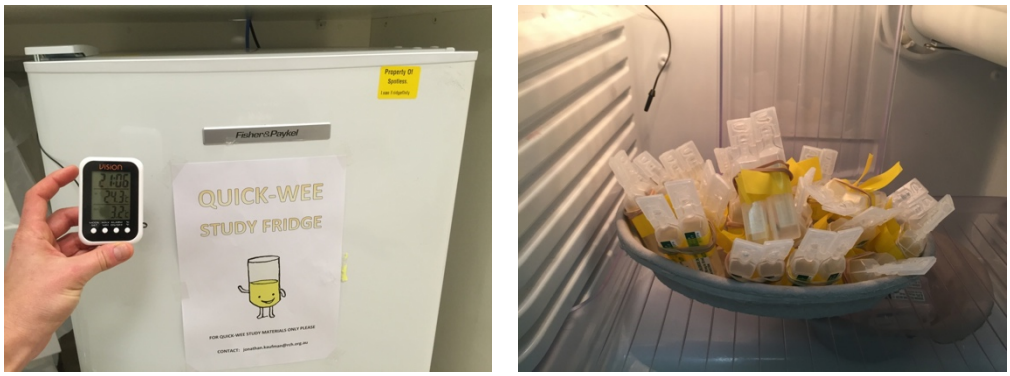
Figure 17: Clinician collecting RCT study equipment



The designated study box and designated study fridge were easily accessible in the ED treatment room.

For pragmatic reasons, it was planned to use different types of fluid ampoules for cleaning and the intervention, to clearly designated the cold intervention fluid within the trial. Room temperature sterile water ampoules were used for perigenital cleaning, as per local clinical practice guidelines. [64] Refrigerated saline ampoules were used for the intervention, as these ampoules have different colour markings and were further labelled with study specific yellow tags.

Figure 18: RCT study refrigerator and study fluid ampoules



The cold fluid ampoules were stored in a designated study refrigerator with a temperature of 2.8°C (Figure 18), checked monthly with an in-situ digital thermometer and recorded in a study log to ensure temperature range +/-1°C.

Clinicians were advised to start using the cold fluid within 2 minutes after being taken out from the refrigerator, to ensure that it remained as close as possible to the designated temperature.

Figure 19: RCT study equipment for urine collection



5.5.4.7 Monitoring of adherence to intervention protocols

Non-adherence to the intervention was defined as discontinuation of the allocated treatment before the child voided urine or before completion of the 5 minute study period.

Adherence was recorded by the treating clinician on the case record form (CRF), and any reasons for non-adherence were recorded. The CRF also contained a section for additional comments from the treating clinician (Appendix 11.3.5).

The study protocol did not include a specific plan for the research team to observe and monitor adherence to the study protocol and the intervention procedures. As this was a straight-forward intervention delivered by the

treating clinicians, it was not considered necessary for researchers to monitor clinician adherence within the trial.

5.5.4.8 Blinding and placebo

The study could not be blinded. While in general a double-blind study design is the gold-standard for a randomised controlled trial, the Quick-Wee intervention has an obvious and visible physical nature. Consequently, it would not be possible to blind participants, caregivers or treating clinicians who were actively involved in the delivery of the intervention. As the primary outcome measure of the trial (voiding urine) is also obvious and completely objective, blinding of the assessors was not necessary.

The study did not include a placebo for the control group. It would be challenging to design and implement a suitable sham or placebo physical intervention for the control group in this study. A placebo intervention would need to resemble a plausible physical stimulation applied to the child, without providing any actual stimulation which could influence the likelihood of voiding. The study team discussed this possibility, and felt that even if possible, it would be unlikely to provide additional rigour to the trial methodology.

5.5.4.9 Randomisation sequence generation and allocation concealment

Study participants were randomly assigned, in a 1:1 ratio, to the intervention (Quick-Wee method) or standard care (routine clean catch). A statistician not involved in the analysis of the study results prepared the randomisation schedule using computer generated random permuted blocks with at least three different block sizes, to ensure concealment of allocation and reduce predictability of the random sequence. Randomisation was not stratified (e.g by age or sex), to maximise the generalisability of findings to everyday clinical practice.

A paper based system was used to designate each infant's allocation in the study, using individual sequentially numbered opaque sealed envelopes prepared by the independent statistician, containing the randomised

allocation. Each individual study pack contained one sealed envelope with the allocation and intervention instructions specific to the allocated group (Appendix 11.3.4). This was opened by the clinician at the patient bedside, immediately before removing the nappy and commencing perigenital cleaning for urine sample collection. Therefore treatment allocation was concealed from clinicians and caregivers during recruitment and consent, and allocation concealment was preserved until immediately before commencement of the allocated intervention at the bedside.

5.5.5 Data collection methods, management and analysis

This section further describes the methods used to ensure accurate data collection, minimise missing data, maximise data quality, and maintain data security.

5.5.5.1 Data collection methods and study instruments

The study data was recorded by clinicians in the ED on paper based case record forms (CRFs). The data from the CRF was then entered by the research team using the REDCap database on the MCRI computer server. The paper based CRF used to record study data is included in Appendix 11.3.5.

5.5.5.2 Data quality measures

Data quality was ensured with rigorously designed processes at multiple levels of data recording, entry and checking including in:

1. The paper CRF used by clinicians in the ED
2. The electronic REDCap study database used by the research team
3. The Stata statistical software package used to analyse data

To ensure accuracy of initial data collection, the CRF was designed to be as straight-forward as possible for clinicians to complete, and utilised predominantly simple tick-box responses or brief open questions. This enabled clinicians to complete the CRF quickly and easily, which was

considered important in the busy ED clinical environment. The CRF was designed by the doctoral candidate and modified with feedback from the study team. The CRF was piloted with 5 ED clinicians prior to commencement of the study using hypothetical patient scenarios, and questions that could have been considered unclear or ambiguous were adjusted.

Research team members used original written CRFs when entering data into the REDCap electronic study database. All data in the database was then checked and verified by a second member of the research team, which was completed by the doctoral candidate and Dr Fitzpatrick. The study database required verification of all inclusion and exclusion criteria and recording of consent for all study participants, as recorded by the clinician on the CRF, to ensure only eligible participants were included in the analysis.

The REDCap study database was designed to allow only reasonable and plausible data entry, primarily using dropdown selection boxes which only allowed for the responses specific to that question. This included several data quality measures, including:

- Mandatory entry fields: prompted user if data not entered
- Binary data: database entry options “yes” or “no”, or “not recorded” or “research team unsure”
- Categorical data: database entry options as specified by question, or “not recorded” or “research team unsure”
- Continuous data: database entry options on scale specified by question, or “not recorded” or “research team unsure”
- Free text: only allowed for designated open questions
- Comments section: available for research team entering data to list any difficulties or clarifications required with the data entry

Further coding rules were developed in REDCap to prevent impossible or conflicting data entry. This included the use of conditional logic, for example a question about time to void would only be applicable if the child voided, so this

question only becomes visible in the electronic database if the preceding question about voiding within 5 minutes was answered as “yes”.

Data entry into the electronic database was then piloted using 5 hypothetical CRFs containing a plausible range of clinical scenarios, and a further 5 hypothetical CRFs containing missing mandatory data and implausible data.

Only designated members of the research team had access to the password protected study database to enter data. The REDCap database allowed the lead researcher to track all data entry, allowing clarifications in the event of any data discrepancy. Only the doctoral candidate had access to subsequently modify or amend entered data if required after data checking. On the few occasions where this was required for minor corrections, the correct data was confirmed with a third member of the research team prior to any corrections being made. A random check of 35 CRFs (10% of total sample) was undertaken, to confirm the accuracy of paper data from CRFs compared to electronic data in the study database.

After the initial data verification from the paper CRF and subsequent verification in the REDCap electronic database, data was imported into spreadsheets in the Stata statistical software program, and visually inspected for plausibility and obvious errors. Data was then checked electronically using formulas for range checks in Stata, to confirm all data for each question was within the expected and possible range for each question.

Raw data was preserved and cleaned data was saved separately, to ensure original data was not altered and remained accessible. Data errors and amendments were automatically recorded within the REDCap system, and noted in a separate paper file.

5.5.5.3 Follow-up of outcome data

CRFs were collected at least 3 times per week by a member of the research team from the designated study box in the ED. CRFs were visually checked at that time for completeness. If CRFs contained incomplete data, a member of

the research team contacted the recruiting clinician as soon as possible in person in the ED. Where this was not possible, the doctoral candidate then contacted the clinician by phone or email. The clinician was asked to complete the missing data where possible. If required, the patient notes in the hospital Electronic Medical Record were checked by a member of the research team to further clarify any missing data.

5.5.5.4 Data management and confidentiality

Paper study records were kept in locked storage cabinets in the MCRI. All electronic participant study records were stored in a password protected computer study database hosted by MCRI, accessible to the researchers only.

All study participants were assigned a unique study number (Subject ID) for the study, so that stored data dispersed to study team members at the end of the study had identifiers removed but was re-identifiable. The document linking the Subject ID with personal identifiers was password protected and accessible only to the researchers from the MCRI computer study database.

The unique Subject ID was used to identify all data from the CRF after clinical and laboratory data entry and cleaning from RCH clinical and laboratory databases into the password protected study database.

To further preserve confidentiality, no individual participant data was used in any presentations or publications arising from the study. Only aggregate data was used.

The data management plan for retaining health information followed the appropriate local legislated requirements. As per these guidelines, the Health Records Act 2001 (Victoria), all health information will be kept until a participant reaches 25 years of age.

5.5.6 Statistical methods

This section further describes the statistical analysis plan including type of analysis for the study as a whole and for study outcomes, and methods to handle missing data.

5.5.6.1 Statistical analysis plan

The statistical analysis plan was developed by A/Prof Donath and the doctoral candidate, with input from all study co-authors.

The primary analysis for the study was an intention-to-treat analysis, including all eligible randomised participants with primary outcome data available. The intention-to-treat analysis is recommended by the CONSORT guidelines as the preferred analysis strategy for randomised controlled trials. [249]

5.5.6.2 Primary and secondary outcome analysis

The analysis plan for primary and secondary outcomes is described in full in both the published protocol paper and the published results paper.

5.5.6.3 Additional analyses

Age and sex (gender) are potential confounders for the outcomes of this study, though previous studies show conflicting results.

Gender differences in the anatomy of the urinary outflow tract between boys and girls may affect the trajectory and velocity of the urinary stream. This could influence the likelihood of successful catching of a urine sample upon voiding.

Gender may also influence the likelihood of sample contamination. Urine has been shown to flush the vagina and foreskin during voiding on micturating cystourethrogram studies, [26] which is a plausible mechanism for contamination in both genders. A gender difference was noted in that study, with flushing visualised in 43% of boys and 14% of girls younger than 12 months. However Alam et al (2005) found the contamination of clean catch

was lower in boys (12%) than in girls (19%), though the difference was not statistically significant (p=0.3). [137] In the preceding baseline study (Chapter 3), girls had a higher proportion of contaminated clean catch urine samples than boys (53% vs 32%, p=0.02). [244]

Age may influence the likelihood of sample contamination, and in the preceding baseline study (Chapter 3) contamination was highest in the youngest age group. However studies of midstream collection in older children show the opposite effect with age. [182]

Stratification of recruitment and randomisation would be one strategy to examine the influence of age and gender on study outcomes. However this would be logistically challenging to implement given the resource constraints of this doctoral research. Therefore it was decided, as well as the unadjusted analysis, to adjust results for primary and secondary outcomes for both age and sex. Linear regression models were used for continuous outcomes (satisfaction measured on a 5 point Likert rating scale) and logistic regression for binary outcomes (voiding urine, collecting a urine sample, sample contamination).

Circumcision status can also influence the likelihood of both UTI, and sample contamination, in boys. However for this trial the study team decided not to specifically consider circumcision status, to preserve the generalisability of study findings. Circumcision status of male participants was not recorded on the study CRF.

5.5.6.4 Withdrawals

Participant caregivers were informed at the time of obtaining consent that they could withdraw from the study at any stage, and this would not in any way affect the treatment or management provided by the treating clinician. If consent was withdrawn, no more data or samples were collected. Data collected prior to withdrawal of consent was retained unless otherwise requested. Withdrawals after commencement of the intervention were not replaced, consistent with the intention-to-treat analysis plan.

5.5.6.5 Missing data and protocol non-adherence

Measures to minimise missing data are described previously in the Data Management section of this chapter. There was minimal missing data in this study. No participants had missing data for primary or secondary outcomes.

However not all patients had a urine sample collected successfully during the 5 minute study period. Additionally, some urine samples were used for bedside dipstick testing but not sent for laboratory culture, at the treating clinician's discretion. Therefore the secondary outcome of contamination was analysed only for patients who had a laboratory culture result, and not considered missing data. Data was analysed without imputing for missing values.

Clinicians recorded on the CRF if any significant problems occurred, or if the intervention was ceased before the child voided or the end of the 5 minute intervention period. After randomisation, three families withdrew consent and requested sample collection by another method (one in the control group and two in the intervention group). These participants were analysed in their assigned groups as per the intention-to-treat analysis. All other participants adhered to the study protocol.

5.5.7 Data monitoring

This section further describes the data monitoring plan for the study.

5.5.7.1 Data monitoring

A data monitoring committee was not required for this low-risk trial.

5.5.7.2 Interim analysis

No interim analysis was performed for this study. It was planned to examine the recorded data after 50% of the sample size was recruited, to assess any need to replace participants with missing primary outcomes. Only the presence or absence of the primary outcome was checked by the doctoral candidate.

5.5.7.3 Harms and adverse events

There were no foreseeable risks to children or their families from the intervention or participating in this study.

An adverse event was defined as any unintended outcome occurring during the study caused by the action or non-action of the intervention, resulting in harm to the participant. Further detail for the definitions of types of adverse events is included in section 4.8.2.8 of the preceding chapter. Adverse events if they occurred were documented on the CRF.

Very minor discomfort for the child may occur with either cleaning the genital area with sterile wash (standard practice), being exposed in the ED with the nappy removed (standard practice) or gentle cutaneous suprapubic stimulation with cold saline soaked gauze (Quick-Wee intervention). Crying commonly occurs with routine non-invasive urine collection and therefore was not regarded as an adverse event, consistent with previous studies. [140 234]

5.5.7.4 Auditing

Trial conduct was audited by the research team by the following measures:

- Inspection of CRFs for missing data and recording of any study withdrawals, protocol violations, adverse events or other difficulties
- Review of trial progress at monthly ED departmental research meetings
- Formal feedback from ED clinicians during study education and promotion sessions
- Informal feedback from ED clinicians to the research team

5.5.8 Methods summary

This study was a large RCT evaluating success to collect non-invasive urine samples within 5 minutes, comparing the novel Quick-Wee voiding stimulation method to standard clean catch practice. The study protocol and methodology was rigorous, following the SPIRIT guidelines. Robust sample size

calculations were based on preceding baseline and pilot studies, and expert clinical opinion to determine a clinically significant effect. The study used an intention-to-treat analysis and focussed on the clinically relevant outcomes of voiding, sample collection and contamination, as well as parent and clinician satisfaction. The study setting in a busy hospital ED with the intervention delivered by clinicians rather than researchers follows real-world practice, enhancing the generalisability of findings to other clinical settings.

5.6 RESULTS

The results for the Quick-Wee RCT are described in this section. This includes the published results paper, as well as further detail and elaboration not included in the published paper which contribute to the interpretation and discussion of the results.

5.6.1 Published results paper (Paper 4)

The results of the trial were published in the journal *The BMJ*, and are included below.

OPEN ACCESS

Faster clean catch urine collection (Quick-Wee method) from infants: randomised controlled trial

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ABSTRACT

OBJECTIVE
To determine if a simple stimulation method increases the rate of infant voiding for clean catch urine within five minutes.

DESIGN
Randomised controlled trial.

SETTING
Emergency department of a tertiary paediatric hospital, Australia.

PARTICIPANTS
354 infants (aged 1-12 months) requiring urine sample collection as determined by the treating clinician. 10 infants were subsequently excluded.

INTERVENTIONS
Infants were randomised to either gentle suprapubic cutaneous stimulation (n=174) using gauze soaked in cold fluid (the Quick-Wee method) or standard clean catch urine with no additional stimulation (n=170), for five minutes.

MAIN OUTCOME MEASURES
The primary outcome was voiding of urine within five minutes. Secondary outcomes were successful collection of a urine sample, contamination rate, and parental and clinician satisfaction with the method.

RESULTS
The Quick-Wee method resulted in a significantly higher rate of voiding within five minutes compared with standard clean catch urine (31% *v* 12%, P<0.001), difference in proportions 19% favouring Quick-Wee (95% confidence interval for difference 11% to 28%). Quick-Wee had a higher rate of successful urine sample collection (30% *v* 9%, P<0.001) and greater parental and clinician satisfaction (median 2 *v* 3 on a 5 point Likert scale, P<0.001). The difference in contamination between Quick-Wee and standard clean catch urine was not significant (27% *v* 45%, P=0.29). The number needed to treat was 4.7 (95% confidence interval 3.4 to 7.7) to successfully collect one additional urine sample within five minutes using Quick-Wee compared with standard clean catch urine.

CONCLUSIONS
Quick-Wee is a simple cutaneous stimulation method that significantly increases the five minute voiding and success rate of clean catch urine collection.

TRIAL REGISTRATION
Australian New Zealand Clinical Trials Registry ACTRN12615000754549.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Urinary tract infection (UTI) is a common early childhood febrile illness, and a urine sample is required for diagnosis or exclusion
Urine sample collection can be challenging in pre-continent children, and current collection methods have limitations
The clean catch urine collection method is recommended by UK NICE guidelines, but can be time consuming or unsuccessful

WHAT THIS STUDY ADDS

A simple suprapubic cutaneous stimulation method using gauze soaked in cold fluid to trigger voiding (the "Quick-Wee" method) significantly increased the voiding and success rate of clean catch urine for infants aged 1-12 months
The Quick-Wee method requires minimal resources and is a simple way to trigger faster voiding for clean catch urine from infants in the acute care setting

Introduction

Urinary tract infections (UTIs) are common in young children, affecting 5-7% of febrile children under 2 years of age.[1 2] Investigation of potential UTIs should be considered in cases of unexplained fever in this age group, as clinical signs may be non-specific.[3 4] The diagnosis of a UTI has important implications for follow-up, and delayed treatment can result in morbidity, including renal scarring[5 6] and serious bacterial infection.[7] Expedient collection of a urine sample allows for dipstick urinalysis and microscopy screening to guide immediate clinical decision making for treatment initiation,[8] although a positive culture result with pyuria is the gold standard for definitive diagnosis.[7] However, obtaining urine from pre-continent children can be difficult and time consuming. Despite urine samples being so commonly required in clinical practice, all current collection methods have limitations. Choosing the method of collection must balance reliability, speed, contamination, and invasiveness. Accordingly, clinical guidelines have differing recommendations,[4 7] clinician preferences vary,[9-11] and ongoing debate about the optimal collection method exists in the literature.[12 13]

Non-invasive methods for urine collection may be regarded as practical and convenient and acceptable for children who do not require urgent antibiotic treatment.[7] Urine collection bags are often used[11 14] but have unacceptably high false positive and contamination rates.[15 16] The culture results from a bag urine sample and antibiotic sensitivities therefore cannot be used reliably to direct treatment. Clean catch urine collection involves waiting for a nappy-free child to void spontaneously, and it is the recommended method of urine collection by the UK National Institute for Health and Care Excellence guidelines.[4] Contamination rates of 5-27% have been reported for clean catch urine,[16-19]

much lower than other non-invasive methods.[15 16 19] In practice though, clean catch urine collection can tie up valuable resources in clinical settings, with average waiting times of 30-71 minutes,[20 21] of which only 64% of first attempts are successful.[21] In contrast to the UK, the American Academy of Pediatrics guidelines recommend non-invasive samples can be used for screening; but an invasive catheterisation or suprapubic aspiration sample is required for definitive diagnosis and before starting antibiotic treatment.[7] Invasive samples have lower contamination rates[16] but cause pain and distress for children and require equipment and technical expertise to collect. For these reasons invasive methods may not be favoured by some clinicians,[9-11] and might be impractical outside hospital settings.[13]

These difficulties with urine sample collection can lead to misdiagnosis or a missed diagnosis of UTI. One study found that 32% of children aged less than 2 years had no urinalysis or culture performed for outpatient UTI episodes treated with antibiotics.[22] An ideal method of urine collection would be non-invasive, fast, gentle, and simple, and such a method has been identified as a priority for future research.[7 23 24] Anecdotally, clinicians may have noted that some children void spontaneously during the routine cleaning of the perigenital area before urine collection. This cold, wet stimulation likely triggers cutaneous voiding reflexes, which remain under-investigated as a mechanism for improved urine collection. In animal studies perigenital-bladder spinal reflexes can be stimulated mechanically or when mothers lick the perigenital skin of their newborns.[25 26] In humans, suprapubic stimulation is proposed to trigger parasympathetic detrusor contraction through the exteroceptive somato-bladder reflex mechanism.[27] We hypothesised that gentle suprapubic cutaneous stimulation using gauze soaked in cold fluid (the Quick-Wee method) might hasten bladder voiding for clean catch urine by triggering early childhood cutaneous voiding reflexes. We evaluated the efficacy of this new voiding stimulation method to increase the rate of urine voiding within five minutes for infants in the emergency department.

Methods

The full study protocol is published and available in an open access journal.[28]

Trial design, participants, and setting

This was a randomised, prospective, non-blinded superiority trial, conducted from September 2015 to April 2016 in a single tertiary paediatric emergency department at the Royal Children's Hospital, Melbourne Australia. The emergency department has 85 000 presentations annually.

Eligible participants were pre-continent infants aged 1-12 months (corrected for prematurity if <36 weeks' gestation) where a urine sample was required and the treating clinician determined clean catch urine to be an appropriate method of collection. Neonates (aged <1 month) were not included as our institution does not recommend non-invasive urine collection to investigate UTI in this age group because of their greater risk of serious bacterial infection. We excluded infants with anatomical or neurological abnormalities affecting voiding or sensation.

No changes to methods were made after the trial commenced. The study is reported in accordance with the Consolidated Standards for Reporting Trials (CONSORT) statement for randomised trials.[29]

Clinicians in the emergency department (nursing and medical) were trained to recruit participants and implement the intervention with face-to-face departmental education sessions and written instructions. Infants suitable for inclusion were identified by clinicians, who made decisions about the appropriate method of urine sample collection on clinical grounds. Suitable participants were recruited consecutively.

We assigned participants randomly, in a 1:1 ratio, to receive either the intervention (Quick-Wee) or usual care (standard clean catch urine with no additional stimulation) for up to five minutes. An independent statistician prepared the randomisation schedule using random permuted blocks with at least three different block sizes to ensure concealment of allocation. Opaque envelopes concealing the allocation, within sealed individual study packs, were used to assign the intervention in the emergency department. Study packs were kept available from a locked study box from which they could only be taken sequentially. Owing to the obvious nature of the intervention, blinding was not possible after randomisation and assignment to intervention.

Interventions

The clinician provided a written study information handout, verbally explained the procedure to the parent/carer, and obtained verbal consent.

The clinician prepared the child for the clean catch urine attempt, opened the opaque randomisation envelope by the bedside, then immediately removed the nappy and started the timer. A parent, carer, or clinician was ready to catch a urine sample if the child voided, and the genital orifice was cleaned for 10 seconds with sterile water at room temperature (standard practice). In the usual care arm the clinician waited for the child to void spontaneously, until clean catch urine was obtained or the timer reached five minutes. In the intervention arm the clinician (or parent/carer with supervision) additionally rubbed the suprapubic area of the child in a circular pattern with gauze soaked in cold saline held with disposable plastic forceps (fig 1), until clean catch urine sample was obtained or the timer reached five minutes. One operator performed the intervention.

The timer was stopped if the child voided and clean catch urine was obtained, and time to void was recorded. Alternatively a missed catch, failure to void at five minutes, or reason for abandoning the procedure was recorded, as well as parental and clinician satisfaction with the method. Children who were randomised and voided during the 10 second cleaning phase (which was part of the total five minute study period) were included in the intention-to-treat analysis.

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Fig 1 | Quick-Wee voiding stimulation method of gentle cutaneous suprapubic stimulation using gauze soaked in cold fluid. Image courtesy of Bill Reid, Royal Children's Hospital creative studio

Standardised urogenital cleaning for both groups was performed using a designated standard cleaning pack with 10 mL sterile water ampoules at room temperature. Additional suprapubic cutaneous stimulation was done using a designated pack containing disposable plastic forceps and gauze, and study labelled ampoules with 10 mL of cold 0.9% saline. The cold fluid was stored in a designated study refrigerator with a monitored temperature of 2.8°C. Clinicians were advised to start using the cold fluid within two minutes of removal from the refrigerator to ensure it remained as close as possible to the designated temperature.

When clean catch urine was not obtained within the five minute trial period, the clinician decided about the ongoing method for urine collection (continue clean catch urine, catheter, suprapubic aspiration sample, or abandon urine collection).

Treating clinicians recorded any adverse events, and intervention could be discontinued.[30] Crying and mild distress commonly occur with routine clean catch urine and were not regarded as an adverse event, consistent with previous studies.[18 20 23 31]

Outcomes

The primary outcome measure was voiding of urine within five minutes (binary yes or no outcome: voided).

Secondary outcome measures were if the child voided, whether any urine was successfully caught in the specimen jar or was missed (binary yes or no outcome: clean catch urine collected if voided), contamination of clean catch urine samples obtained within five minutes (binary yes or no outcome: urine culture contamination as per hospital laboratory definition, ≥3 colony types with colony forming units (CFU) $\geq 10^6$/L, or ≥2 colony types with CFU $\geq 10^7$/L where the predominant organism was a contaminant), and parental and clinician satisfaction with the urine collection method (5 point Likert satisfaction rating scale).

Data collection

Clinicians in the emergency department recorded data on paper case record forms. The data were then entered by the research team into the REDCap (Research Electronic Data Capture) electronic database.[32]

Demographic and participant data recorded included age, sex, relevant medical comorbidities, previous UTI, clinical indication for urine collection as recorded by the clinician, and reasons for exclusions and refusals.

Clinical data recorded included whether the child voided within five minutes, and time taken to void; successful catch of urine sample if voided; person performing the standardised cleaning (parent, doctor, or nurse); person performing the suprapubic stimulation in the intervention group (parent, doctor, or nurse); person catching the urine (parent, doctor, or nurse); adverse events; whether the urine collection attempt was abandoned before five minutes and, if so, reason for abandonment; and parental and clinician satisfaction with the urine collection method.

Clinical data collected subsequently by the research team (by linking with laboratory data and hospital records) included positive and contaminated urine culture results, admission to hospital, and start of antibiotic treatment.

Sample size calculation

A sample size of 354 participants (177 in each group) was based on power calculations using data from planned preceding baseline and pilot studies. An initial prospective observational baseline study determined the success of standard clean catch urine in young pre-continent children, and in preliminary data children aged <12 months 21% (12/57) voided within five minutes.[33] We surveyed a panel of 20 expert clinicians (paediatric emergency doctors and paediatricians at consultant level) who reported an increase in success rate of approximately 15% compared with standard clean catch urine collection would suggest that a simple technique such as Quick-Wee should be incorporated into their clinical practice. A pilot study of the new method showed that Quick-Wee was a feasible and acceptable intervention to obtain clean catch urine within five minutes.[30] Thirty five per cent (7/20) of children voided using cold temperature saline for stimulation, suggesting that a difference of approximately 15% was a reasonable estimate of the treatment effect. Most successful voids were from infants

aged 1-12 months, an age group that was therefore chosen for the definitive trial.

A sample size of 322 participants (161 in each group) was required to have 80% power to detect a difference between groups of 21% (non-intervention arm) versus 35% (intervention arm) for voiding within five minutes. Power and sample size calculations were completed using an estimated total sample size for a two sample proportions test (Pearson's χ^2 test). An additional 10% of participants (16 in each group) were included to account for a small loss to follow-up of primary outcome results. Analysis was by intention to treat, consistent with CONSORT guidelines.[29 34]

Statistical analysis

For the primary outcome we report rates of voiding urine within five minutes for each group with percentages, the absolute difference for percentage voiding between groups, and 95% confidence intervals for each, and we calculate P values using a χ^2 test. We considered a P value <0.05 to be significant. For secondary outcomes we report the rates of successful urine collection and contamination for each group with percentages and 95% confidence intervals, and median and interquartile ranges for parental and clinician satisfaction. The appropriate difference between groups was reported (difference of proportions for categorical outcomes, difference of medians for skewed continuous outcomes), together with the 95% confidence interval for the difference. We estimated P values using χ^2 for categorical variables and *t* test or Wilcoxon rank-sum tests for continuous variables.

In addition to the unadjusted analysis, all treatment comparisons for primary and secondary outcomes were adjusted for age and sex to account for any chance imbalance between the treatment groups with respect to these potentially confounding factors, using quantile and logistic regression models for continuous and binary outcomes, respectively. Statistical calculations and analyses were completed using Stata 14 (Stata Corp, TX). No interim analysis was performed.

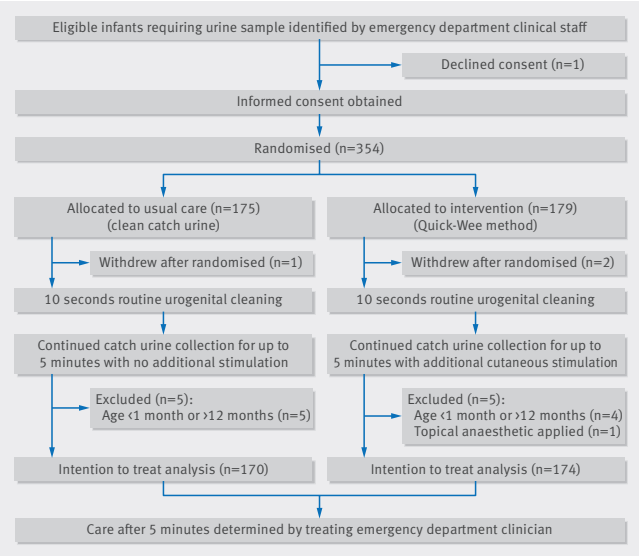


Fig 2 | **Flow of participants through study**

Patient involvement

Feedback from the parents and carers of 40 participants in the preceding pilot study contributed to refinement and confirmation of the study research question and outcome measures. Parents and carers were asked to rate their satisfaction with the intervention and could provide additional comments. Parental satisfaction with the intervention in the pilot study was high and no respondents were dissatisfied with the intervention,[30] demonstrating feasibility for this larger definitive trial.

Patients were not further involved in the design, recruitment, and conduct of the study. The burden of intervention was assessed with a parental satisfaction rating using a 5 point Likert scale, which was a secondary outcome measure of this study. Results of this study will be available to the wider community, including study participants, through publication in an open access journal.

Results

Overall, 354 participants were recruited and 10 were excluded (fig 2): five were aged less than 1 month, four were aged more than 12 months, and one had topical anaesthetic cream applied for a suprapubic aspiration procedure that affected sensation. One family declined consent to randomisation, and three families withdrew consent and requested sample collection by another method (one in the control group and two in the intervention group). No adverse events occurred during the trial, and no participants had missing primary outcome data. Two infants (0.6% of participants) in the intervention group voided during the 10 second cleaning procedure and were included in the intention-to-treat analysis.

Of 344 participants included in the analysis, 172 (50%) were male with a mean age of 5.4 months (table 1). Clinical indications (could be ≥1) for urine collection were predominantly fever of unknown origin (n=144, 42%), unsettled baby (n=132, 38%), poor feeding (n=76, 22%), specifically suspected UTI (n=60, 17%), and vomiting (n=27, 8%). Thirty three infants (10%) had medical comorbidities (table 1). A UTI was present in eight of 55 infants (14%) with laboratory culture results available, defined as growth of a uropathogenic organism with CFU $\geq 10^8$/L.

A total of 127 clinicians recruited one or more participants for the trial (n=60 (47%) nursing, n=67 (53%) medical), and subsequently allocated roles for the procedure. Clinicians primarily performed the routine urogenital cleaning of the 354 infants in the trial (n=152 (43%) nursing, n=174 (49%) medical, n=28 (8%) parent) and the Quick-Wee method for the 174 infants

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Table 1 | Demographic and clinical characteristics of participants. Values are number (percentage) of participants unless stated otherwise

Characteristics	Quick-Wee (n=174)	Standard clean catch urine (n=170)
Male	95 (55)	77 (45)
Mean (SD) age in months	5.4 (3.2)	5.4 (3.0)
Previous UTI	10 (6)	15 (9)
Antibiotics in past 24 hours	9 (5)	10 (6)
Comorbidities:		
Minor renal anomaly	8 (5)	7 (4)
Congenital cardiac	3 (2)	1 (0.6)
Seizure disorder	3 (2)	0 (0)
Genetic syndrome	0 (0)	2 (1)
Gastro-oesophageal reflux	2 (1)	2 (1)
Other	3 (2)	2 (1)
Indication for urine sample*:		
Fever of unknown origin	78 (45)	66 (39)
Unsettled baby	66 (38)	66 (39)
Poor feeding	33 (19)	43 (25)
Specifically suspected UTI	29 (17)	27 (16)
Vomiting	17 (10)	10 (6)
Failure to thrive	1 (1)	7 (4)
Metabolic/electrolyte/jaundice	0 (0)	3 (2)
Haematuria	2 (1)	1 (1)
Other	6 (3)	6 (4)
Hydration state:		
Normal	120 (69)	132 (78)
Mild	48 (28)	33 (19)
Moderate	5 (3)	2 (1)
Severe	0 (0)	1 (1)

UTI=urinary tract infection.
Apparent discrepancies are due to rounding.
*More than one indication may be selected.

in the intervention group (n=89 (51%) nursing, n=82 (47%) medical, n=3 (2%) parent). Parents primarily collected the urine of the 74 infants who voided within the five minute trial period (n=13 (18%) nursing, n=8 (11%) medical, n=46 (62%) parent, n=7 (9%) not recorded).

Compared with standard clean catch urine, Quick-Wee had a higher rate of voiding within five minutes (table 2). In total, 54 out of 174 infants (31%) voided within five minutes in the Quick-Wee group, compared with 20 out of 170 (12%) in the standard clean catch urine group. The difference in proportions for the primary outcome was 19% favouring Quick-Wee (95% confidence interval for difference 11% to 28%), with a risk ratio of 2.6.

Compared with standard clean catch urine, Quick-Wee had a similarly higher rate for successfully catching a urine sample and also higher parental and clinician satisfaction with the method of urine sample collection (table 2). The rate of contamination between groups was not statistically significant, with lower numbers for this outcome because not all participants had a urine sample processed for culture (table 2). The number needed to treat to successfully collect one additional urine sample within five minutes using Quick-Wee compared with standard clean catch urine was 4.7 (95% confidence interval 3.4 to 7.7).

After adjustment for age and sex the primary outcome results were unchanged (data not shown). Risk difference and confidence intervals for successfully catching urine and for contamination, and difference in medians for parental and clinician satisfaction with the method, were also unchanged when adjusted for age and sex.

Discussion

Gentle suprapubic cutaneous stimulation with gauze soaked in cold fluid (the Quick-Wee method) led to a clinically and statistically significant increase in voiding and successful urine collection within five minutes for infants aged 1-12 months. The difference in contamination was not significant as confidence intervals overlapped, potentially due to lower numbers of available culture results. Importantly, parents and clinicians preferred the Quick-Wee method, reporting higher satisfaction than with standard clean catch urine.

Strengths and limitations of this study

To our knowledge this is the first randomised trial to demonstrate the efficacy of a voiding stimulation method for infants. Strengths of this study include the preceding baseline and pilot feasibility studies, its large sample size, and randomised study design. More than 100 clinicians in the emergency department rather than dedicated research staff performed the intervention, and all eligible infants were included regardless of feeding and hydration state, minimising

Table 2 | Primary and secondary outcomes

Outcomes	Quick-Wee (n=174)	% (95% CI)	Standard clean catch urine (n=170)	% (95% CI)	Difference in proportions or medians (95% CI)	P value
Primary outcome:						
Voided <5 mins	54/174	31 (24 to 39)	20/170	12 (7 to 18)	19 (11 to 28)	<0.001*
Secondary outcomes:						
Voided and successful catch	52/174	30 (23 to 37)	15/170	9 (5 to 14)	21 (13 to 29)	<0.001*
Contamination†	12/44	27 (15 to 43)	5/11	46 (17 to 77)	18 (−14 to 50)	0.29‡
Median (interquartile range) parent satisfaction§	2 (1-3)		3 (2-3)		1 (0.6 to 1.4)	<0.001¶
Median (interquartile range) clinician satisfaction§	2 (1-3)		3 (2-3)		1 (0.6 to 1.4)	<0.001¶

*χ^2 test.
†Small proportion of samples in each group not sent for culture by treating clinician.
‡Fisher's exact test.
§5 point Likert scale: 1=very satisfied, 2=satisfied, 3=neutral, 4=unsatisfied, 5=very unsatisfied.
¶Wilcoxon rank sum test.

selection bias and ensuring the generalisability of results. The method is simple and does not require any specialised equipment so it can be utilised in low resource settings as a successful example of frugal innovation.[35] This study has some limitations. Given the obvious nature of the method it would not be possible to blind clinicians to the intervention. Neonates and pre-continent children aged more than 12 months were not included in the study.

Comparison to other studies

Previous randomised studies have examined novel methods to obtain more rapid clean catch urine in pre-continent children. These include a vibrating bladder stimulator for infants and toddlers in the emergency department (not effective)[20] and lumbar/bladder stimulation for neonates in the neonatal intensive care unit (effective but limited to neonatal age group and setting).[18]

Three decades ago Taylor et al tested the concept of triggering voiding using a finger tap method, although this study was limited by not recording the time taken to void in over half the infants in the study and by lacking a comparison group.[36] The lumbar/bladder stimulation method subsequently described by Herreros et al has been shown to have a promising success rate of 78-86% for clean catch urine within five minutes in a neonatal intensive care setting.[18 31] However, participants in these studies had a mean age of 7 or less days, urine was predominantly collected for reasons other than investigation of UTI or fever, and infants with poor hydration and feeding were excluded. This may limit the generalisability of these findings to children in the primary or acute care setting, who are predominantly older and often unwell and poorly hydrated when a UTI is suspected. The lumbar/bladder stimulation method also requires infants to be held up suspended under the arms while stimulation manoeuvres are performed and catching a sample is attempted. This technique requires two or three staff members,[18 23 31] and may be less feasible in larger and heavier infants.[37]

The lumbar/bladder stimulation method has recently been investigated in three non-randomised trials for infants in the emergency department and was found to have a lower success rate in this population. Valleix et al obtained clean catch urine within five minutes in 27% of pre-continent children aged more than 1 month, with difficulties managing the children's position in 46% of the participants.[37] Labrosse et al obtained clean catch urine within five minutes in 49% of younger infants aged less than 6 months.[38] Tran et al used a different method of two three-minute stimulation attempts separated by a 30 minute interval of bag urine collection during which the infant was given water, formula milk, or breast milk.[23] Although results are thus not directly comparable, the study found an overall success rate of 40.9% for 142 non-ambulant infants aged less than 2 years, which reduced with age, from 88.9% (newborn) to 28.6% (age >1 year). All three studies reported greater success in younger infants. This reduced potency in older infants may be expected given the hypothesis of stimulating newborn cutaneous voiding reflexes, which diminish with age.[39]

The contamination rate for the Quick-Wee method (27%) is similar to that reported in previous voiding stimulation studies (16%,[38] 24%,[18] and 38%[23]). Exact microbiological definitions of contamination, however, are not established in the literature and guidelines and vary between laboratories and institutions and thus may not be directly comparable. Clinical decisions about specimen collection and treatment in the presence of contamination should consider the clinical context, urinalysis, and the presence or absence of pyuria on microscopy.

Cold thermal stimulation has been suggested to pose a risk of cold burns to sensitive skin[20]; however, in the 174 infants in the intervention arm of the current study there were no such adverse events and there was high parental and clinician satisfaction associated with stimulation using gauze soaked in cold fluid refrigerated to a temperature of 2.8°C.

Unanswered questions and future research

This trial used gauze soaked in cold fluid for stimulation over a period of five minutes. We used saline for the stimulation fluid so that ampoules could be easily identified in the trial, but any clean cold fluid could be used. Although our pilot study suggested that cold stimulus was more effective than stimulus at room temperature,[30] future trials examining the temperature of stimulation applied to trigger voiding or a repeated application of the stimulation may further enhance the success of this method. Children in the neonatal age range were not included in the trial, but younger infants have been shown to be more responsive to stimulation of newborn cutaneous voiding reflexes.[23 37 38] This method could be further evaluated for neonatal patients where urine is being collected for reasons other than investigation of a UTI. We hypothesised that stimulating faster and more forceful voiding may reduce sample contamination, and although contamination was lower with the intervention this did not reach statistical significance. Contamination of clean catch urine may be related to urine flushing of the foreskin or vagina, which is seen on micturating cystourethrogram,[40] and higher contamination has been found from initial void rather than midstream samples.[41] Future research to further reduce the contamination of clean catch urine by incidental skin flora, such as through standardised methods to clean the perigenital area,[42] may be of additional benefit.

Conclusions and implications for clinicians and policy makers

UTI is common in unwell young children presenting to primary and acute care, but reaching or excluding the diagnosis is not straightforward.[2 43 44] Collecting urine samples from young pre-continent children is challenging and the limitations of existing methods are well

known. National Institute for Health and Care Excellence guidelines on UTI recommend clean catch urine collection, although in practice, attempts can be time consuming or unsuccessful.[21] Voiding stimulation methods such as Quick-Wee can enhance clean catch urine collection by increasing the speed and success of obtaining urine. Timely collection of specimens is important and has many benefits, including expediting patient progress and clinical decision making in primary and acute care settings, reducing unnecessary or broad spectrum antibiotic treatment,[22] preventing morbidity from UTI, and limiting unnecessary representation and follow-up to health services for missed diagnosis and misdiagnosis. Voiding stimulation methods could be easily incorporated into urine collection strategies in guidelines and clinical practice where non-invasive collection is indicated. Where appropriate this may spare some children the pain and distress associated with catheter and suprapubic aspiration procedures. The Quick-Wee method requires minimal resources and is a simple way to trigger faster voiding for clean catch urine from infants in the acute care setting.

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Ethical approval: The study protocol (HREC reference 35083A) was approved by the Royal Children's Hospital human research ethics committee. All participants gave informed consent.

Data sharing: No additional data available.

Transparency: The manuscript's guarantors (JK and FEB) affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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5.6.2 Reporting guidelines: CONSORT

The relevant international reporting guideline was followed when writing the results paper for the Quick-Wee RCT.

The Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement is an internationally recognised guideline for the reporting of randomised controlled trials, particularly for individually randomised two-group parallel trials. [250] CONSORT is an evidence-based set of minimum reporting guidelines for randomised trials and includes a 25-item checklist outlining how the trial was designed, analysed and interpreted, and flow-chart showing how participants progressed through the trial. [250] The Quick-Wee RCT was reported following the CONSORT Statement. The CONSORT flow-chart is included in Figure 2 of the published paper, [251] and the full checklist was submitted with the study manuscript at the time of publication.

5.6.3 Harms and adverse events

No adverse events occurred during the trial.

For three participants (1 in the control group, 2 in the Quick-Wee group) it was documented on the CRF that the infant was unsettled and crying with the intervention. Consent was withdrawn from ongoing participation in the study for these 3 participants, and data was analysed in the group they were assigned to as a treatment failure (did not void urine within 5 minutes).

As described a priori in the methods of the trial, crying and mild distress routinely occur during urine collection and were not regarded as an adverse event, consistent with previous studies. [140 234]

No other difficulties were recorded in the trial.

5.7 DISCUSSION

5.7.1 Overview

This randomised trial provides definitive evidence for the Quick-Wee voiding stimulation method. Quick-Wee increases the rate of voiding and successful urine sample collection within 5 minutes for infants aged 1-12 months. Caregiver and clinician satisfaction was higher for Quick-Wee than for standard practice. These results were statistically and clinically significant. Contamination was lower with Quick-Wee than with standard practice, however this result was not statistically significant due to the lower number of samples obtained and sent for culture.

This section discusses the validity, strengths and limitations of the study, and comparison to other voiding stimulation methods and previous studies.

5.7.2 Validity

The word “valid” is derived from the Latin “validus” and French “valide”, meaning strong. The validity of a research trial determines its strength and quality.

5.7.2.1 INTERNAL VALIDITY

Internal validity refers to the design and conduct used to minimise the possibility of bias of the study findings. [252] Internal validity can be influenced by random error, confounders and bias.

5.7.2.2 Random error

Random error can affect internal validity, causing inconsistency across the sample. Random error is a product of innate human variability and chance, and is by its nature random and unpredictable, and therefore difficult to control. [253]

The Quick-Wee study was designed to minimise the likelihood of random error in four ways. Firstly, the sample size was adequately large to give precision to the estimation of the treatment effect, calculated based on robust data from prospective pilot and baseline studies. The Quick-Wee study is the largest ever study of a voiding stimulation method for young children (n=344 participants, compared to n=142 in the next largest study). Secondly, the study protocol was published in advance, with strong adherence to the protocol. All participants received the intervention they were assigned to receive, and all participants received identical care except for their designated intervention. Thirdly, reliable outcome measures were used, which were either binary and objective (voiding urine, collecting urine sample, sample contamination), or used validated measurement tools (5 point Likert Scale measuring caregiver and clinician satisfaction). Fourthly, data accuracy was maximised with rigorous data recording, entry and checking procedures.

5.7.2.3 Confounders

Confounding can occur when factors that are different between groups influence the association between the exposure and outcome. Confounding is minimised by randomisation. [253]

In the Quick-Wee RCT, groups were generally balanced in terms of baseline characteristics. Mean age was the same in both groups (5.4 months). There were slightly more males in the Quick-Wee group (55%) compared to the standard Clean Catch control group (45%). There were slightly more children with abnormal hydration status in the Quick-Wee group (31%) compared to the control group (21%).

Further, regression analysis to account for factors which have been shown in the literature to influence outcomes (age, sex) did not alter the study findings.

5.7.2.4 Bias

Bias is a non-random deviation of results or inferences from the truth, [253] or processes leading to such deviation.

Selection bias can occur if eligible participants are deliberately excluded from recruitment and enrolment and the study investigator knows which group the participant would have been allocated to had they been enrolled. For example in a study where voiding of urine is the primary outcome, excluding participants who are poorly hydrated who would have been allocated to the intervention group may increase the success rate of the intervention, as poorly hydrated children may be less likely to void.

Selection bias in the Quick-Wee RCT was minimised with randomisation and allocation concealment. Randomisation in a 1:1 ratio ensured that participants were equally likely to be allocated to the two possible study groups. The randomisation schedule was prepared by an independent statistician using random permuted blocks in at least 3 different block sizes, to prevent study investigators or clinicians guessing the pattern of allocation.

Allocation was concealed right up until the moment of the intervention. Sealed opaque envelopes were contained within individual study packs, which could only be taken sequentially from a locked study box, concealing the treatment allocation. The allocation envelopes were opened at the bedside, in front of caregivers and other clinical staff, so all were aware of the treatment allocation.

Ascertainment bias can occur when knowledge of which intervention the participant was receiving distorts interpretation of results. The obvious nature of the Quick-Wee intervention meant that blinding was not possible in this trial. However the use of objective and binary outcome measures in the study methods in this study minimised the risk of ascertainment bias.

Attrition bias can occur when background and results data is missing from the study analysis. Some missing data is inevitable when conducting research in a real-world clinical setting. Participants may also drop out before the end of the trial, or not adhere to study procedures. All participants in the Quick-Wee trial received the intervention they were allocated to.

No participants had missing data for primary or secondary outcome measures. However not all participants actually had a urine sample collected during the 5 minute study period, and not all collected urine samples were sent for culture (at the treating clinicians' discretion), so contamination data was not available for all participants.

Only three participants (3 of 344, <1%) withdrew consent during the intervention (one in the control group, and two in the Quick-Wee group). All participants were analysed by intention-to-treat analysis in the groups in which they were allocated.

5.7.2.5 EXTERNAL VALIDITY

External validity refers to the applicability or generalisability of the study findings to other patients and settings. [252] The Quick-Wee trial was specifically designed to maximise generalisability of findings, so that clinicians could consider using the method in their own setting.

5.7.2.6 Study setting

Firstly, the study took place in a 'real-world' setting, conducted in a busy hospital ED. The intervention was implemented in the ED during day and night time, and under circumstances with the same pressures on staff, time, and hospital bed occupancy that typically occur in the hospital setting.

Given the trial was conducted with limited funding and resources, the trial setting in the ED was highly practical, as the large ED census allowed for timely recruitment of participants over a 7 month study period.

5.7.2.7 Recruitment by ED clinicians

Secondly, recruitment and the study interventions were carried out by ED clinicians, rather than by dedicated members of the study research team. 127 nurses and doctors recruited one or more participants for the trial (n=67 doctors, 53%, and n=60 nurses, 47%). Members of the study research team recruited only a small number of participants (11 of 344, 3%), which only occurred during their usual duties as clinicians working in the ED.

This is a significant strength compared to most previous studies of voiding stimulation methods. In most previous studies the interventions were carried out by a small research team, [140 234 236 239] or it is not specified whether the clinicians who carried out the interventions were part of the research team. In only one study, by Valleix-Leclerc et al, was the intervention carried out by general nursing staff in the ED for the 48 participants in that trial. [240] Having dedicated researchers recruit and perform the interventions may introduce a risk of an unconscious bias into recruitment and study implementation.

5.7.2.8 Representative study population

Thirdly, study participants were representative of the many young children who require urine sample collection to diagnose or exclude possible UTI. Inclusion criteria in the Quick-Wee RCT were broad, including children where the treating clinician felt that urine sample collection was required, and if clean catch was an appropriate collection method. Exclusion criteria were narrow.

5.7.2.9 Appropriate age of study participants

Infants less than one month of age were excluded from the Quick-Wee study, as in our institution guidelines do not recommend non-invasive collection for unwell infants in this age group. [64]

Previous studies of the bladder-lumbar stimulation method have all included infants less than one month of age, and have reported success rates as high as 78-86% within 5 minutes in the neonatal setting. [140 234] Inclusion of the neonatal age group is an important consideration when comparing success rates between studies and between methods. Voiding stimulation methods rely on triggering newborn voiding reflexes, and newborn reflexes diminish with age. It could therefore be postulated that a higher success rate would be found in neonates, and that excluding neonates in the Quick-Wee trial could have reduced the overall success rate of the method.

In studies of the bladder-lumbar stimulation method where both neonates and older infants are included, success was significantly higher for the neonates than for the older infants, [236 239 240] decreasing from 89% in neonates to 29%

in children >1 year in one study. [239] However in the Quick-Wee RCT the regression analysis for age did not change results, which was an unexpected finding.

5.7.2.10 Inclusion of infants with poor feeding and hydration

Infants with poor feeding and dehydration were included in the Quick-Wee RCT.

It would be expected that dehydration would reduce bladder volume and therefore make voiding less likely. It could be postulated this increased the previously reported success rates for the bladder-lumbar method, where poorly hydrated or poorly feeding infants were deliberately excluded from most studies of that method. [140 141 234 237 240 241]

In the Quick-Wee RCT, an “all-comers” approach was specifically chosen, reflecting real world practice, where clinicians frequently have to collect urine samples from children regardless of their feeding and hydration status.

5.7.3 Strengths and limitations

5.7.3.1 STRENGTHS

This study had a number of strengths, in general and in comparison with previous studies.

5.7.3.2 Preceding baseline and pilot study

The Quick-Wee RCT was preceded by pre-planned baseline and pilot feasibility studies. Both of these studies have been published. [244 246] These preceding studies allowed robust calculation of the RCT sample size, and refinement of study methods.

5.7.3.3 Randomisation

The Quick-Wee RCT is the first randomised trial to show efficacy of a voiding stimulation method for infants aged 1-12 months.

Only two previous trials of voiding stimulation methods have been randomised, as described in section 4.7. Davies et al (2018) investigated the use of a vibrating bladder stimulator device for infants in the ED (n=97), [127] which was shown to be ineffective. Altuntas et al (2015) investigated the bladder-lumbar stimulation method for neonates in the Neonatal Intensive Care Unit (n=127) [140] finding the method was successful in this much younger age group, however neonates with poor feeding or hydration were excluded from that trial.

5.7.3.4 Control group

The Quick-Wee RCT included a control group. Apart from the two randomised trials by Davies et al and Altuntas et al, [127] [140] no other studies of voiding stimulation methods included a proper control group or comparison population. It is therefore not known how many children would have voided without the intervention in those studies.

5.7.3.5 Sample size

This trial (n=344) is the largest ever study of a voiding stimulation method. A larger sample size allows for greater precision in estimating the size of the treatment effect.

5.7.3.6 Rigorous methodology

The Quick-Wee RCT followed all standards for randomised trials as per the CONSORT guideline. [250] The study protocol was published in advance, [254] and the trial did not deviate from the planned methodology. The statistical analysis for primary and secondary outcomes was an intention-to-treat analysis. All participants had primary outcome data available.

5.7.3.7 Generalisability

As described in the validity section above, the study setting and study participants reflect real-world patients in a real-world setting. The intervention was performed by clinicians, not researchers. In particular, all appropriate infants who required a clean catch sample were included, as determined by their treating clinician, regardless of their hydration and feeding status.

5.7.3.8 Measurement of caregiver and clinician satisfaction

The Quick-Wee RCT is the only trial of a voiding stimulation method to measure and report the satisfaction of caregivers and clinicians with the method.

5.7.3.9 LIMITATIONS

Like any research, this study also has some limitations.

5.7.3.10 Generalisability

There are some limitations to the generalisability of the study findings. The study was conducted in a tertiary paediatric hospital ED. The ED environment has some differences compared with the paediatric ward environment, though they are broadly similar.

The ED is a very different environment compared to the primary care setting though, with significant differences in staff, time and equipment availability. The findings as such may not be immediately generalisable to the primary care setting. These differences between the hospital and primary care setting are explored further in the qualitative study in Chapter 7. However the patient population across these settings, while not exactly the same, is likely to be broadly similar. It could be postulated that infants in the ED may tend to be sicker than infants in the primary care setting, and therefore the method may even be more efficacious in primary care, though this is entirely speculative.

5.7.3.11 Blinding

Given the obvious nature of the Quick-Wee method it was not possible to blind clinicians to the intervention.

5.7.3.12 Age range

As previously stated, infants <1 month of age (neonates) were not included in this study. This is because non-invasive urine sample collection for sick neonates is not recommended in guidelines at our institution.

Children >12 months were not included in this study. This was because in the preceding pilot study, very few children >12 months voided with the Quick-Wee intervention. The study team therefore decided to limit participation to infants <12 months in the RCT. This also fits with the underlying physiology of newborn voiding reflexes, which like other newborn reflexes likely diminish with age over the first year of life.

5.7.3.13 Contamination

Not all infants in the Quick-Wee RCT had a urine sample collected during the 5 minute study period, and a small number of urine samples were dipsticked by the treating clinician but not sent for culture.

Therefore although contamination was lower in the Quick-Wee group (12 of 44, 27%) compared to the clean catch group (5 of 11, 46%), these numbers were small and the trial was inadequately powered to detect a significant difference for this outcome, and 95% confidence intervals were broad and overlapped (15-43% vs 17-77%).

5.7.4 Comparison to other voiding stimulation methods

Historical studies of the bladder finger-tap technique have methodological limitations, [232] [233] and the technique has been incorporated into the more recently described bladder-lumbar stimulation method.

A vibrating bladder stimulator device has been shown to be ineffective at increasing the rate of voiding for infants in the ED. [127]

The bladder-lumbar stimulation method has been evaluated in multiple previous studies. While differences in study populations and study methodologies limits direct comparison of outcomes, this method is the most well studied voiding stimulation method and so was used for qualified comparison in the following sections.

5.7.4.1 Single vs multiple operators

Only one operator is required to perform the Quick-Wee method. This is a significant strength compared to the bladder-lumbar stimulation method, which requires 2-3 operators to suspend the child under the armpits while the stimulation is performed.

Both methods can utilise an additional assistant to catch the urine sample when the child voids, which could in practice be a parent.

5.7.4.2 Equipment

The Quick-Wee method does require some very basic equipment, however only gauze and cold fluid are needed, both of which are cheap and easily accessible in nearly any clinical setting.

We chose to use gauze and saline ampoules in the study as they are readily available and were practical given the study methodology. However the gentle suprapubic stimulation could likely be performed by parents with many other similar items in the home setting, such as a small face-washer and cold water.

5.7.4.3 Positioning

The Quick-Wee method is performed with the child in the supine position. This is easy for the clinician, comfortable for the child, and allows a parent to be close to provide comfort and re-assurance to the child.

The bladder-lumbar stimulation method as described by Herreros is performed with the child suspended “under their armpits with their legs dangling”. [234] While this may be easy with smaller neonates, it is likely to be more challenging in older and heavier infants. This difficulty with positioning was reported in the study by Valleix-Leclerc et al (2016), where “difficulties maintaining the child in the correct position due to weight were reported for 22 cases out of 48, i.e 46% of the patients analysed”, as well as “struggling children” reported for 14 out of 48 cases (29%). [240] Tran et al (2016) also found that heavy weight and infant discomfort were predictors of failure in their study. [239]

5.7.4.4 5 minute voiding success

In this RCT, the Quick-Wee method had a 5 minute voiding success rate of 31%, compared to 12% with standard clean catch practice. Comparison to other voiding stimulation studies is limited due to substantial differences in the study participants and study methodologies between trials.

Only one study of the bladder-lumbar stimulation method is randomised, with a success rate of 78% for the intervention. [140] However the study population in the Altuntas et al trial (2015) is very different to the study population for the Quick-Wee trial. Participants in that study were neonates in a NICU setting with a mean age of 7.5 days old. Babies with poor feeding and hydration were excluded. Most (two thirds) of the study participants were having urine samples collected due to hyperbilirubinaemia, with relatively few having urine collected due to features of potential UTI. The success of the bladder-lumbar stimulation method in the Altuntas trial was 78%, compared to 33% in the control group. Interestingly, these are both approximately 2.5 times proportionately greater than the intervention and control success rates of the Quick-Wee trial (78 vs 31% and 33 vs 12% respectively). This may reflect the increased strength of newborn voiding reflexes in neonates compared to older infants.

Studies of the bladder-lumbar stimulation method outside the NICU setting are not randomised. The lack of random allocation and lack of control group limits the opportunity for direct comparison to the Quick-Wee RCT. Non-randomised studies by Valleix-Leclerc et al (2016) and Labrosse et al (2016), which used the common 5-minute primary outcome timeframe, reported success rates of 27% and 49% respectively. [236] [240] However the Labrosse trial only included infants up to 6 months of age. Tran et al used a different methodology of two 3 minute stimulation periods separated by a 30 minute period of bag urine collection, and did not utilise an intention-to-treat analysis, [239] finding a success rate of 41% for voiding during the two 3 minute periods. Nikam et al (2017) used a much longer 15 minute time period for the intervention with a success rate of 70% for infants up to 6 months of age, but excluded infants with poor hydration. [241]

5.7.4.5 Contamination

Comparison of sample contamination between studies is limited for a number of reasons. Firstly, definitions of contamination vary between laboratories and centres, limiting direct comparison. Secondly, only the Altuntas trial had a control group, so the baseline contamination rate of routine clean catch for all other studies of the bladder-lumbar stimulation method is not known. Thirdly, many trials of the bladder-lumbar stimulation method do not report on contamination at all.

5.7.4.6 Systematic review of voiding stimulation methods

A recent systematic review published in January 2020 evaluated the evidence for voiding stimulation methods used for urine sample collection in pre-continent children. [243] The review authors identified 3 randomised studies evaluating 3 different methods, being the vibrating bladder stimulator device and the bladder-lumbar stimulation method described previously in section 4.7, and the Quick-Wee method. [127 140 251]

The review noted the Quick-Wee RCT sample size was approximately three times larger than both other RCT sample sizes (n=344, n=127 and n=97 respectively). Using the Cochrane Risk of Bias tool, no risk of bias was identified for the Quick-Wee RCT, whereas both other RCTs had an unclear risk of bias in one or more areas.

The review authors described the Quick-Wee RCT as “the most recent and rigorous of these” randomised trials, and noted that “interventions requiring more than two operators are likely to reduce the generalisability and applicability irrespective of their clinical effectiveness owing to the resource and time implications of using multiple members of staff.”

Overall study quality was graded using the Downs and Black score (Table 4), with the Quick-Wee RCT being graded in the excellent/good range and the other two RCTs being graded in the fair range.

Table 4: Quality assessment of voiding stimulation RCTs

Study	Method	Sample Size	Downs & Black Score
Kaufman et al 2017 [251]	Quick-Wee	n=344	24
Altuntas et al 2015 [140]	Bladder-lumbar stimulation	n=127	15
Davies et al 2008 [127]	Vibrating bladder stimulator device	n=97	17

Summarised from Tables 1&3: Chandy et al, EMJ 2020 [243]
Downs and Black score: excellent/good = 20–28; fair = 15–19; poor = <14.

5.7.5 Implications for practice and further research

5.7.5.1 Clinical utility

The Quick-Wee method is simple to perform. This makes the method suitable to use in a broad range of clinical settings, including in the emergency department, hospital paediatric wards, and in primary care. In particular, the Quick-Wee method may be useful in settings where invasive sample collection methods are not possible or practical.

Caregivers and clinicians also reported higher satisfaction using the Quick-Wee method compared to standard clean catch, indicating its acceptability.

5.7.5.2 Frugal innovation for resource limited settings

"Frugal innovations" are inexpensive but effective solutions to providing healthcare to patients in low resource settings. [51] They may be imperfect, but they are suited to use in constrained environments.

The Quick-Wee method requires no special training, and no specialised equipment is required. This makes it ideally suited to use in resource-limited settings, as a successful example of frugal innovation. Frugal innovations

"often represent alternatives with excellent cost–benefit ratios adapted to their contexts". [51]

5.7.5.3 Costs

The Quick-Wee method requires little equipment. The increased success and time-savings of the method would be expected to reduce the overall costs of ED presentations for infants where urine sample collection is required. However, staff time to explain and perform the intervention could increase costs. Therefore a health economic evaluation comparing the cost-effectiveness of existing urine sample collection methods and the Quick-Wee method is necessary. This is explored further in the next chapter.

5.8 CHAPTER SUMMARY

The primary aim of this chapter was to determine if the Quick-Wee voiding stimulation method increases the rate of voiding urine within 5 minutes compared to standard clean catch for children aged 1-12 months

In this large and rigorous RCT, the Quick-Wee method has been shown to be three times more effective, and also more acceptable, than standard clean catch collection. The method is simple and was easily performed by clinicians in the busy ED setting of this trial. As not all participants voided during the 5 minute intervention period, the trial was unable to draw conclusions about contamination.

The cost-effectiveness of the method is explored subsequently in Chapter 6.

Implications for policy and practice are discussed in Chapter 9.

Chapter 6 LIQUID GOLD: HEALTH ECONOMIC EVALUATION

"Why is urine yellow? Because it is liquid gold!"
(paediatric nephrologist Dr William Primack)

Roberts (2015) [22]

6.1 OVERVIEW

This chapter describes the second part of the thesis research, the Liquid Gold health economic evaluation.

Sections 6.2 – 6.7 include the rationale for the research, background and literature review specific to the economic evaluation, aims, hypothesis, and methods.

Sections 6.8 - 6.9 includes results and the published outcomes paper, and additional results not included in the published paper which contribute to interpretation of the chapter results.

Section 6.10 discusses the strengths and limitations of the study, the place of this study in the context of the broader literature, and implications for policy and practice.

PAPER 5: ECONOMIC EVALUATION

The published economic evaluation (Paper 5) forms part of this chapter:

5. **Kaufman J**, Knight A, Bryant P, Babl F, Dalziel K. Liquid gold: the cost-effectiveness of urine sample collection methods for young precontinent children. *Archives of Disease of Childhood*, 2020;105:253-259: doi: 10.1136/archdischild-2019-317561

6.2 RATIONALE

Chapter 2 of this thesis established that paediatric UTI is a common infection of early childhood, and the signs of UTI in young children are non-specific. Therefore many young children require evaluation for potential UTI. Collecting a urine sample is mandatory to diagnose or exclude UTI, but existing collection methods have varying success rates and resource requirements, and therefore are likely to have different costs.

Chapters 4 and 5 of this thesis have shown that the Quick-Wee voiding stimulation method is acceptable and effective. However it is not known if it is cost-effective in comparison to existing collection methods.

Optimised urine sample collection is a potential avenue to reduce healthcare costs from paediatric UTI, particularly for young children where collection can be challenging. Accurate knowledge of the costs of urine sample collection methods could inform practice, policy and guideline recommendations to achieve cost savings.

This economic evaluation therefore focuses on the crucial first step for evaluating paediatric UTI in young pre-continent children, which is collecting a urine sample. Though costs are likely small for individual patients, for such a common condition, even small cost savings could be substantial in the aggregate.

6.3 BACKGROUND

As described previously in section 2.5, the total costs of investigating and managing childhood UTI are substantial at a healthcare system level. There are multiple aspects of care that present opportunities for cost savings through evidence-based management. Developing cost-effective strategies to evaluate and treat childhood UTI is accordingly recognised as a research priority. [205] The research in this chapter considers cost-effective urine sample collection as one such opportunity for cost savings.

A urine sample and culture is required to diagnose UTI, and is recommended by all major paediatric UTI guidelines. [12 16 23 186 189] However the signs of UTI in young children are non-specific, so the diagnosis must also be considered in any young child with unexplained fever, not just those with UTI symptoms. Therefore many young children with UTI require urine sample collection to make the diagnosis, and many more febrile young children will also require urine sample collection to exclude the diagnosis. Collecting urine samples from young children is a high burden problem.

Clinicians have differing preferences, [134 142] and guidelines have conflicting recommendations, [23 186] for the optimal method of urine sample collection. Different collection methods have different resource requirements, rates of success and contamination, and therefore are likely to have different costs. The health service resources required comprise the equipment used, clinical staff time, and bed occupancy in hospital or consulting room occupancy in primary care. Additional parental and carer resources may be used and costs incurred such as lost time from paid and unpaid work and out-of-pocket expenses.

The literature review that follows identifies what is known regarding the costs of collecting urine samples, and highlights the knowledge gap and rationale for undertaking this economic evaluation of urine sample collection methods.

6.4 LITERATURE REVIEW: COSTS OF COLLECTION METHODS

A targeted literature review was undertaken by the doctoral candidate, to identify published studies specifically reporting the costs of urine sample collection methods used in young pre-continent children.

Ms Poh Chua, RCH Senior Librarian, provided assistance with designing and refining the literature review strategy.

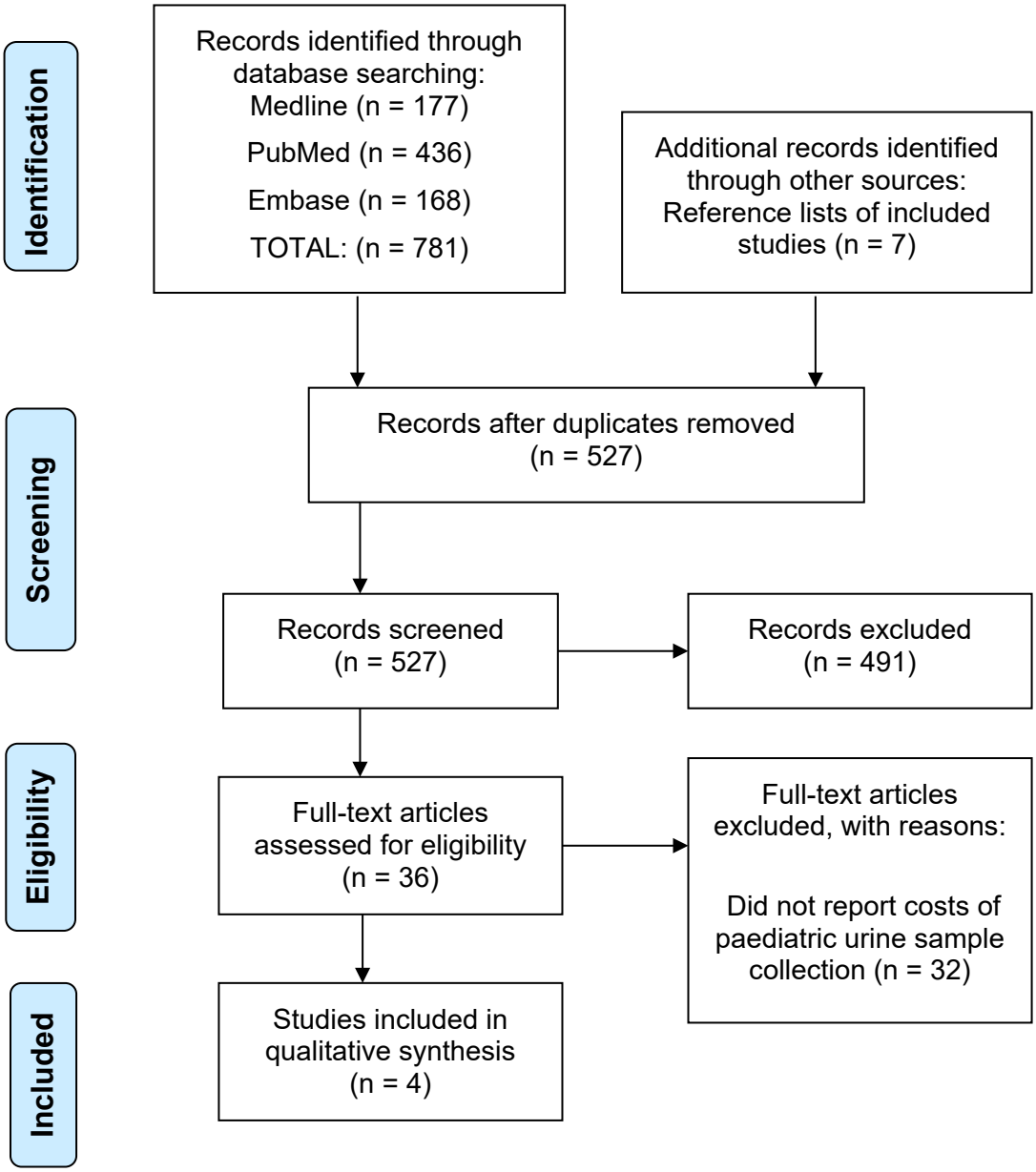
Databases searched included Ovid Medline, PubMed and Embase. Further targeted searching from reference lists and relevant guidelines was

performed. While search terms varied slightly between databases, they effectively focused on the terms “child”, “urinary tract infection”, “urine specimen collection”, “costs”, “expenditure”, “cost analysis”, “economic model” and “economic evaluation”. Full details of the search strategy and search terms is included in Appendix 11.6.2.

Studies were included in the final evidence summary if they reported actual or estimated costs for urine sample collection methods used in young pre-continent children.

Figure 20: Economic evaluation: literature search summary

PRISMA flowchart [231]



4 studies and reports were identified. Each was conducted in different settings, using different approaches. Only one study reported on any actual collection costs, which was based on observations within a research study setting. [31]

6.4.1.1 Evidence summary: costs of urine sample collection

Table 5 summarises the costs of urine sample collection as reported in the published literature.

Table 5: Evidence summary of costs of urine sample collection

Study/report	Study Type & Aims	Participants & Setting	Costs Results	Comments
Downs, 1999, Technical Report: Urinary Tract Infections in Febrile Infants and Young Children [255]	Conceptual model for alternative management strategies of UTI in infants. Aim was to provide evidence to inform recommendations for the American Academy of Pediatrics UTI Guideline.	Analysis conducted by the UTI Subcommittee of the AAP Committee on Quality Improvement Population of interest was children aged 2 months to 2 years examined because of unexplained fever, in the US Healthcare system. Cost data were derived from literature where available, the University of North Carolina Hospital accounting department, and the national physicians' fee schedule.	The economic modelling considered the additional costs of collection using urine bags compared to catheterisation, based on false-positive cultures leading to unnecessary antibiotic treatment and urinary tract evaluation. At the baseline estimate of 70% specificity for bag urine collection, the additional cost of culturing urine specimens obtained with bags rather than by catheterisation was $429.	Actual costs of urine sample collection were not reported.
Hay, 2016, The Diagnosis of Urinary Tract infection in	Decision analytic model based on data from the DUTY study and	Children aged less than 5 years in a multicentre UK	Average time taken and costs for a urine sample with and	Cost of urine sample collection was based on 6

Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness [206] **and** **Hollingworth, 2017, The Diagnosis of Urinary Tract Infection in Young Children (DUTY) Study Clinical Rule: Economic Evaluation** [31]	wider literature, to estimate cost-effectiveness for a two-step clinical rule using symptoms, signs and dipstick testing to guide UTI diagnosis and management in acutely unwell young children presenting to primary care.	primary care cohort study. Participants had an acute illness and at least one potential marker for UTI. Study setting included NHS 'first-point-of-contact' primary care sites, including 225 GP practices, 4 paediatric EDs and four walk-in centres across England and Wales. Costs data for urine sample collection was based on observations from the DUTY study and expert opinion for the GP time required to assess and act on culture results.	without a dipstick test was 12 minutes (costing £8.10) and 9 minutes (costing £7.03) respectively. It was assumed that GPs spent 45 seconds interpreting laboratory results (costing £2.42) and 5 minutes contacting parents to revise antibiotic prescriptions (costing £16.08).	time and motion observations of two nurses collecting urine samples as part of the DUTY study, to estimate the time taken and resource required for urine sample collection. Nurses provided instruction but collection was carried out by parents, either in the clinic or at home. Samples were collected by clean catch, urine pads or urine bags. Age of study participants included children up to 5 years, therefore 'clean catch' samples in this study included involuntary voided samples from younger pre-continent children and also voluntary voided samples from older continent children.

National Institute for Health and Care Excellence, 2017, Resource impact report: Urinary tract infection in under 16s: diagnosis and management (CG54) [208]	Report evaluates the resource impact of implementing the NICE 2017 guideline on urinary tract infection (UTI) in under 16s.	Modelled 2 scenarios for the use of dipstick testing for infants and children 3 months or older but younger than 3 years with suspected UTI.	Estimated costs of initially diagnosing UTI was £38.52, based on the cost of dipstick, microscopy and laboratory culture for a child managed in an outpatient setting.	Did not include costs for actual sample collection.

This literature review has highlighted the evidence gap regarding the costs of urine sample collection methods used for young pre-continent children. The evidence gap means that current guideline recommendations for urine sample collection are not informed by robust evidence of cost-effectiveness. [31]

While a number of factors contribute to the costs of urine sample collection, no previous studies have examined these comprehensively. Accurate cost and cost-effectiveness data that allows comparison between each collection method could inform clinical decision making and guideline recommendations.

The lack of relevant costs data specific to urine sample collection methods is addressed in this economic evaluation.

6.4.1.2 Summary of background and literature review

Collecting a urine sample is the common starting point of evaluation for every child with potential UTI. Timely collection of a reliable sample allows for UTI to be diagnosed or excluded. Failed collection attempts or contaminated specimens corrupt the diagnostic process. The choice of collection method is therefore pivotal to appropriate subsequent management, and may influence short and longer term costs.

The actual costs of urine sample collection in young pre-continent children are not known though. Different collection methods exist, with varying success rates and resource requirements, and therefore different costs. Guideline recommendations for collection methods are not informed by evidence of cost-effectiveness. Urine sample collection is a high burden problem, but under-investigated opportunity for cost savings.

This economic evaluation therefore focuses on the costs of collecting urine samples from young pre-continent children.

6.5 AIMS

6.5.1.1 Primary Aim

The primary aim of this economic evaluation was:

I. To determine the costs and cost-effectiveness of commonly used urine sample collection methods for young pre-continent children in the hospital setting.

6.5.1.2 Secondary Aims

Secondary aims of this economic evaluation were to:

I. Include in the analysis the costs of initial sample collection, as well as projected costs for collecting a definitive sample incorporating the progressive dipstick screening, culture, contamination and patient progress that are used by clinicians to reach a conclusive clinical decision.
II. Compare the cost and cost-effectiveness of the new Quick-Wee voiding stimulation method to existing collection methods.
III. Estimate the potential health service cost savings from cost-effective sample collection at a hospital and national level.

6.6 HYPOTHESES

I. Urine sample collection is a multi-stage process, moving sequentially from the initial collection attempt (which may or may not be successful) through to successful collection of a definitive uncontaminated sample.
II. Each collection method has different resource use, and different probabilities for success at each stage, resulting in different costs and cost-effectiveness for each method.
III. The cost of urine sample collection comprises a moderate proportion of the total presentation costs for young children presenting to the ED with UTI.
IV. The Quick-Wee method is more cost-effective than standard care using clean catch collection, and use of the Quick-Wee method could generate worthwhile cost savings at a healthcare system level.

6.7 METHODS

Methods for the economic evaluation are described in the published paper, with additional detail and explanation described below.

6.7.1 Economic evaluation definitions

6.7.1.1 Heath economic evaluation

Economic evaluations are used to assess new interventions and technologies, and can be used to allocate limited resources. [256] Health economic evaluations use various methods to compare the costs and consequences of different health therapies or interventions. [256 257] Decision tree models can be used as a way of visualising alternatives and incorporating probabilities and assumptions. [256] The aim is to maximise health gains with the available healthcare resources.

6.7.1.2 Cost-effectiveness analysis

A cost-effectiveness analysis is a method to determine the relative value of different programs or interventions. Two (or more) interventions can be

compared when there is a common and measurable outcome for the interventions being evaluated. [256] The results of the cost-effectiveness analysis are only as strong as the underlying evidence used to inform the analysis. The analysis requires a specific perspective, such as the healthcare provider (e.g hospital costs) or the patient (e.g time and out of pocket expenses).

6.7.2 Reporting guidelines: CHEERS

The doctoral candidate followed the relevant international reporting guideline when designing the study protocol and reporting the Liquid Gold economic evaluation.

The Consolidated Health Economic Evaluation Reporting Standard (CHEERS) Statement is an internationally recognised guideline for the reporting of economic evaluations of health interventions. [258] The CHEERS checklist with the 24 guideline items and corresponding page numbers was submitted with the study manuscript at the time of publication.

6.7.3 Study design

6.7.3.1 Roles and responsibilities

The doctoral candidate was the lead researcher responsible for designing, co-ordinating and implementing the economic evaluation. This included developing the model, undertaking all data collection, and performing all analyses.

Health economists Dr Joshua Knight and A/Prof Kim Dalziel advised on the study design and methodology, supervised development of the model, and supervised the costs and cost-effectiveness analyses.

Clinicians A/Prof Penelope Bryant and A/Prof Franz Babl advised on clinical aspects of the model design.

The doctoral candidate wrote the first and final versions of the study protocol, ethics application and manuscript, which were reviewed by all co-authors.

6.7.3.2 Choice of study setting and perspective

The study setting was the ED of the Royal Children's Hospital (RCH). A hospital ED setting was chosen for two reasons.

Firstly, most previous published studies have been conducted in hospital settings, including the preceding Quick-Wee RCT. Therefore most data from the literature used to inform model probabilities was derived from hospital settings. Using a hospital setting allowed for the closest possible consistency of settings for data sources used for the model.

Secondly, urine sample collection occurs frequently in the ED setting. This allowed for sufficient opportunities of direct observation during prospective process mapping, to record actual resource use for both non-invasive and invasive collection methods. This direct observation of urine collection processes for all methods would be less feasible in a primary care setting, particularly for catheter and SPA procedures.

The model accordingly adopted a hospital health-service costs perspective.

6.7.3.3 Choice of collection methods included in the model

The ideal model would include all collection methods used for young pre-continent children to collect urine samples to evaluate possible UTIs. Methods commonly recommended in international guidelines include urine bags, clean catch, catherisation and SPA. [12 23 60 186 187] These four methods were included in the model.

Voiding stimulation techniques are recommended in some recent guidelines, including both the Quick-Wee and bladder-lumbar stimulation methods. [16 104 189 259] Each method has different resource requirements and success rates. However the Quick-Wee method is supported by evidence from an RCT in the ED setting, whereas the bladder lumbar method has not been evaluated in

randomised trials outside the neonatal intensive care setting. Therefore the Quick-Wee method was selected as the preferred voiding stimulation technique for this modelling, and included as a fifth method.

Nappy pads, cotton-wool balls and washed potties are other non-invasive collection methods that may be used in some settings. [145] NICE guidelines mention nappy pads as an acceptable alternative if clean catch is unobtainable, [186] and pads have been used in previous published studies in the primary care setting. [42 43 260] However these methods are not generally used in the ED setting, and have high contamination compared to clean catch. [139] The use of cotton-wool balls is specifically discouraged in NICE recommendations. [186] Therefore this modelling did not include these methods.

6.7.3.4 Scope of the economic evaluation

Cost-effective urine sample collection offers two potential avenues for cost savings:

1. Reducing costs of initial UTI evaluation for many children (low individual cost but high frequency problem)

That is the focus of this economic evaluation. Every child with UTI must have a urine sample collected to confirm the diagnosis, and many other children with unexplained fever must have a sample collected to exclude the diagnosis. Sample collection is mandatory for these two large groups of children.

2. Avoiding unnecessary costs from UTI misdiagnosis which leads to an unnecessary cascade of treatment interventions and further investigations for some children (higher individual cost but lower frequency problem)

This cost saving is implied by improved collection but is challenging to quantify, measure and model. It is beyond the scope of this thesis, but is a valuable topic for future research.

6.7.3.5 Modelling software

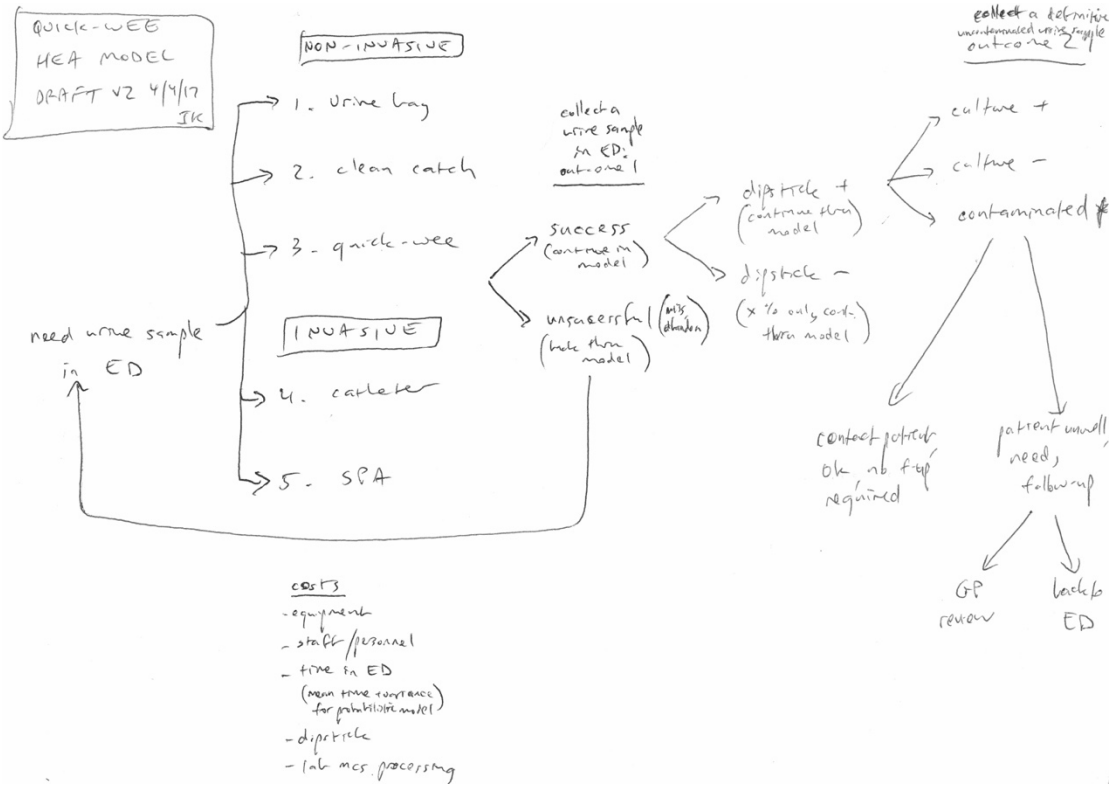
TreeAge Pro is a decision analysis software tool, [261] used for this economic evaluation to perform decision tree model building, cost-effectiveness analysis and sensitivity analyses. The doctoral candidate received assistance from health economists Dr Knight and Mr Max Catchpool for advanced functions of TreeAge Pro.

6.7.4 Modelling and collection of existing data

6.7.4.1 DEVELOPMENT OF THE PROBABILISTIC DECISION TREE MODEL

This analysis considered urine sample collection from young pre-continent children performed to evaluate potential UTI in the ED. The time horizon evaluated was the time from beginning the initial sample collection attempt until reaching the health outcome of interest, which was a clinically definitive decision to diagnose or exclude UTI. In practice, reaching a definitive clinical decision involves several sequential stages.

Figure 21: Draft of decision model

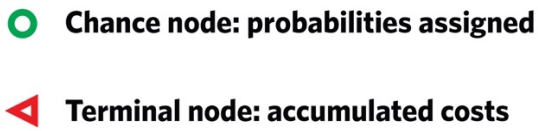


The initial model outline was drafted on paper by the doctoral candidate (Figure 21), to establish a preferred structure reflecting usual clinical practice. Early iterations were refined with assistance from health economists Dr Knight and A/Prof Dalziel, and input from clinicians.

The final decision tree model was then constructed by the doctoral candidate using TreeAge Pro 2017. [261] This was a three stage probabilistic decision analytic model, reflecting real-world clinical processes.

The model begins with branches and a decision node for each collection method option. Sub-branches then follow the possible outcomes. Probabilities are assigned at each chance node, and accumulated costs are assigned at each terminal node (Figure 22).

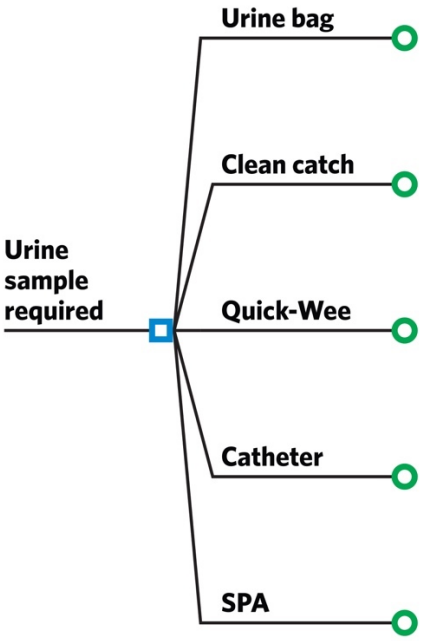
Figure 22: Model nodes



6.7.4.2 Stage 1: Initial collection attempt

The first stage is attempting to collect a urine sample using the collection method selected by the clinician (Figure 23). Selecting the preferred method may incorporate factors such as local guideline recommendations, the child's age and clinical condition, clinician skill and experience, parental preferences, time and resource availability.

Figure 23: Initial collection attempt

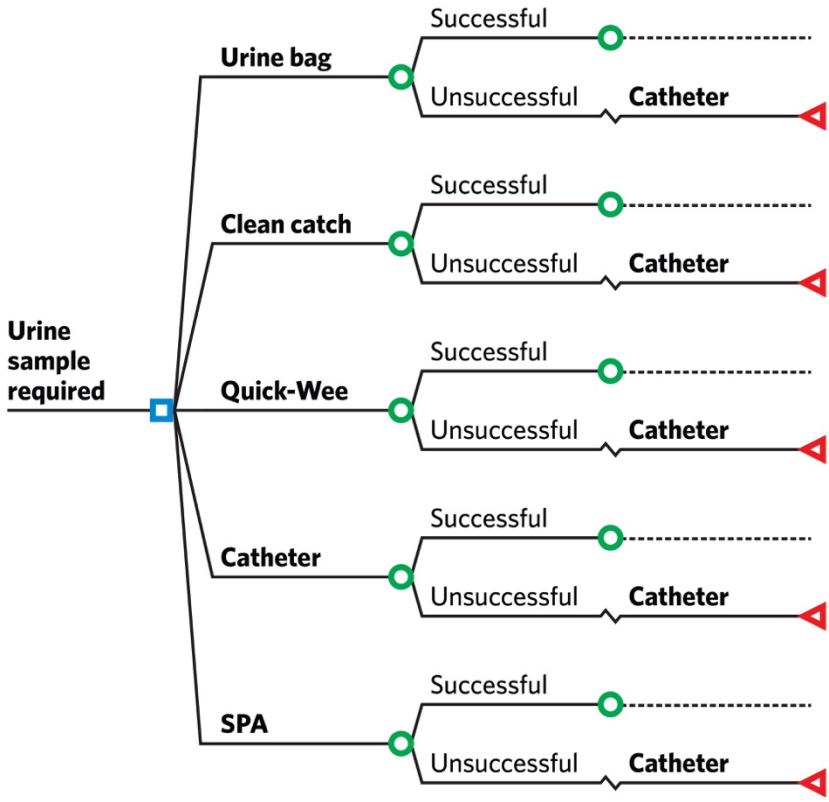


The initial collection attempt may or may not be successful in actually obtaining a urine sample. Collection success rates for each method as reported in the literature were assigned to the model accordingly.

6.7.4.3 Stage 2: Urine sample collection

The second stage is immediately obtaining a urine sample by another means if the initial collection attempt was unsuccessful (Figure 24).

Figure 24: Urine sample collection



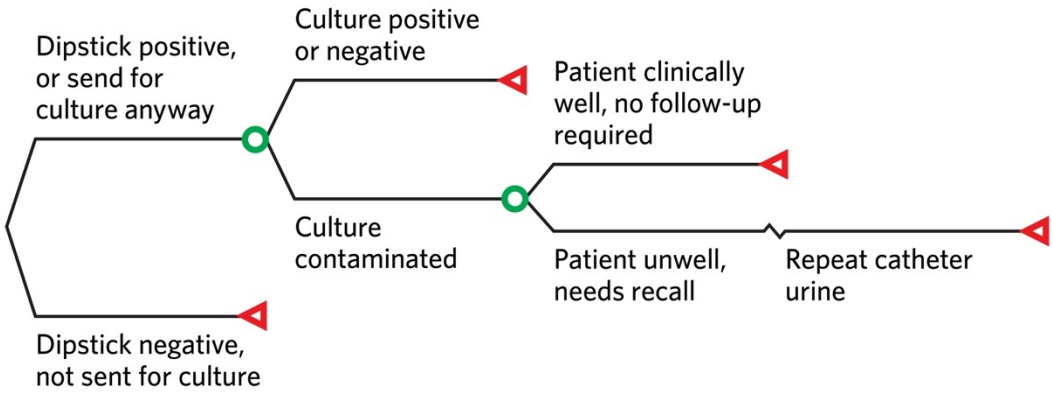
In real-world practice, second collection attempts may incorporate a variety of strategies. These include optimising hydration to increase urinary volume, retrying collection by the same method, changing collection method, asking parents to continue the collection attempt at home, or abandoning collection entirely. However it is not possible to faithfully capture all possible clinical variation within the constraints of a model.

Catheterisation by an experienced operator has a high success rate, [128] and can obtain a urine sample even if there is a low bladder volume. [16] In previous studies catheterisation has been shown to be 100% effective at obtaining urine even after unsuccessful collection attempts with another method. [148] Therefore it was assumed that if initial collection attempts were unsuccessful, the clinician would move directly to collection by catherisation, and this would be successful. This assumption does not reflect the variability of clinical practice that occurs in real life, but was a necessary simplification to complete the model.

6.7.4.4 Stage 3: Reaching a definitive clinical decision

After a urine sample has been obtained, the final stage is the clinician reaching a definitive decision to exclude or diagnose UTI, considering the progressively available clinical information (Figure 25).

Figure 25: Definitive sample collection



Dipstick screening is commonly used to guide initial management of suspected UTI. The dipstick result can indicate if a UTI is likely, or unlikely, and results are available very quickly at the bedside. When there is a low clinical probability of UTI, the dipstick screen may provide sufficient information for the clinician to exclude UTI. Consequently, some urine samples that are obtained will not be sent for urine culture confirmation. However as described in Chapter 2, both false-positive and false-negative results can occur with dipsticks, such as with sterile pyuria or non-nitrite producing uropathogens. Therefore when there is a high clinical probability of UTI, the clinician may send the urine sample for culture even if the dipstick screening result is negative.

When the urine sample is sent for laboratory culture, results will indicate if there is no growth (excludes UTI), positive culture (confirms UTI diagnosis if there is growth of a uropathogenic organism in sufficient quantity), or a contaminated culture (unable to diagnose or exclude UTI because of mixed growth of >1 organism). For this model, it was assumed that urine cultures would have a binary result being either positive/negative (clinician can

definitively diagnose or exclude UTI) or contaminated (cannot diagnose or exclude UTI).

When culture results are contaminated, the clinician must consider two possibilities. The first is that the patient does not have a UTI, and all bacteria grown from the culture are incidental skin flora organisms. The second is that the patient does have a UTI, and that a true uropathogen is concealed amongst other bacteria. In practice, culture results take 24 hours or more to be processed. Clinical progress over that time may inform subsequent decision making. It is usual practice in our ED setting for a consultant emergency physician to follow-up all contaminated culture results with a phone-call to the child's parents. If the child is well, and has not been treated with antibiotics, the clinician may feel that UTI is not likely, and the child can be monitored at home. Alternately the child may remain unwell, but another clinical focus may have emerged, such as the development of diarrhoea suggesting a viral gastro illness. However if the child remains unwell and UTI is still considered a potential diagnosis, they may require recall to the ED for review and repeat sample collection. In this model, it was assumed that a second 30 minute ED presentation would be required for this, to collect an additional urine sample by catheterisation.

Other laboratory results that can contribute to clinician decision making to diagnose or exclude UTI include the serum white blood cell count and C-reactive protein level. However these results are not central to the diagnostic process, and are not specific for UTI, therefore were not included in this modelling.

6.7.4.5 Summary of the model

To summarise the probabilistic model, a patient moves through the decision tree and the three stages of the initial collection attempt, collecting a urine sample by catheterisation if the initial attempt was unsuccessful, and the progressive dipstick and culture results, until reaching a definitive clinical end point of UTI diagnosis or exclusion. The full model is shown in Figure 2 of the published manuscript (Paper 5).

6.7.4.6 DATA ESTIMATES: PROBABILITIES, RESOURCES AND COSTS

Data required to inform the model was obtained by the doctoral candidate and data collection was performed as follows.

6.7.4.7 Resource use for each collection method

Urine sample collection uses resources including equipment, staff time, and hospital bed occupancy. Resources were identified and measured prospectively using process mapping, as described subsequently.

6.7.4.8 Costs data

Data used to value resources were obtained from local sources, reflecting actual costs in the study setting. Data sources are specified in Table 2 of Paper 5. Costs were obtained in 2016 Australian dollars ($AUD), and therefore did not require adjustments such as discounting or inflation.

Costs data for staff time were obtained from the relevant health professional body Employment Award Agreements for nurses and doctors. The mean level of staff experience was estimated by consensus of the clinicians in the research team. Face-validity for these estimates was confirmed with senior clinical members of the department.

Costs data for hospital bed occupancy was obtained from data provided by the Victorian Department of Health and Human Services. This was a summary of average costs per presentation per minute for non-admitted ED patients, specific for the study setting at the RCH.

6.7.4.9 Literature synthesis for model probabilities

At each chance node in the model, probabilities were assigned. This included probabilities for the likelihood of a collection attempt being successful, the likelihood of a collected sample being sent for laboratory culture, the likelihood of a sample being contaminated, and the likelihood of a patient needing recall to the ED if the sample is contaminated.

As described in Paper 5 and reported in Table 1 of that paper, these probabilities were obtained from the published literature. A targeted literature review was performed by the doctoral candidate for each required data point. Where more than one study reported a probability of interest, larger studies or studies in settings most closely reflecting the research setting were prioritised.

A small number of probabilities were not available from the published literature. Where this occurred, the mean value from a survey of 20 expert clinicians was used to establish the probability of interest. The survey is described in more detail below in section 6.7.6, and is reported in the supplementary table (online supplement) of the published paper.

6.7.4.10 SOURCES OF DATA FOR OVERALL UTI BURDEN AND COSTS

Further data was collected to estimate the scale and costs of the UTI and urine sample collection burden in young children, at both a local and national level. This data was not used directly in the model, but was used to estimate the individual hospital and national scale of potential cost savings described in section 6.9 of this chapter. The acknowledgements of the published paper includes the people who provided assistance obtaining this data.

6.7.4.11 ICD-10 coding of data

Patient hospital episodes were identified using World Health Organisation International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes.

Children with a diagnosis of UTI were identified from the following codes:

i. Infection urinary tract (N39.0)
ii. Pyelonephritis (N12)
iii. Pyelonephritis - acute (N10)
iv. Cystitis (N30.9)
v. Cystitis - acute (N30)

Children with unexplained fever (who often require urine sample collection) were identified from the code:

i. Pyrexia of unknown origin (R50.9)

6.7.4.12 Sources of local hospital costs data: RCH

The RCH Decision Support Unit provides analytical and business support to the hospital, including costing data for patient episodes. Data was obtained for non-admitted patients, and separately for admitted patients, aged 0-24 months for the 2016-2017 financial year, diagnosed with either UTI or unexplained fever. Hospital bed occupancy in minutes and average hospital costs was obtained for these patients.

The RCH Pathology Department provided further data for the number of urine culture tests performed in the hospital laboratory, and for the collection method used where this data was recorded on the pathology request form.

6.7.4.13 Sources of national Australian hospital data: IHPA

The Independent Hospitals Pricing Authority (IHPA) is a government body that collects national costing data for hospital patients in Australia. 2016 summary data was obtained for the number and average costs of Australian paediatric hospital presentations and admissions for UTI and unexplained fever.

6.7.4.14 Sources of national Australian primary care data: Medicare

Medicare is the Australian universal health system, which is publicly funded by the Australian Government. The Medicare Benefits Schedule (MBS) is a listing of rebatable services provided in the community such as clinician visits, pathology and imaging tests. 2016 national summary data was obtained for the total number of urine cultures performed for children aged 0-24 months where MBS item number 69333 (urine culture) was claimed.

However MBS data does not include any public hospital patients (neither inpatients or outpatients), for whom pathology tests are paid for by block

funding from the hospital and state government. As such, MBS data will not capture any children who have a urine sample collected in hospital settings.

6.7.5 Process mapping

Different collection methods have different processes and resource requirements including staff time, equipment and bed occupancy. The exact resource requirements for each collection method have not been previously reported or compared, and therefore were recorded by the doctoral candidate using process mapping.

Process mapping is a technique used to document the processes of a defined journey. [262] The processes are the series of steps required to achieve a specified result or outcome. [263] The process map considers each step in the pathway, incorporating data collection and other information relevant to each step. [264] Analysing this information can provide insight with regard to the quality and costs of the activity. [262]

The goal of this process mapping was to quantify the sequential steps, time and resource use of each urine sample collection method included in the economic evaluation.

Prior to data collection the doctoral candidate informally “walked the patient journey” and observed clinical practice. [264] The patient journey was followed for each collection method, and discussed with staff in the clinical environment. This identified the specific equipment, staff and resource items to be quantified. Walking the patient journey informed development of a process map template, to record the relevant data.

The prospective process mapping to quantify resource use was then completed by directly observing and recording 10 episodes of each collection method for clean catch, voiding stimulation, catheterisation and SPA (Paper 5 online supplementary Appendix 2). A Casio timing device was used to record the duration of processes. It was not possible to observe bag collection as this

method is not performed in the RCH ED. Estimated resource use for bag collection was therefore based on assumptions following usual clinical practice in other settings.

All 40 episodes of process mapping were completed and recorded by the doctoral candidate.

6.7.6 Survey of expert clinicians

A survey of 20 expert clinicians was conducted to confirm face-validity of the model, and to ascertain expert opinion for model probabilities that could not be obtained from the literature. Survey methods are described further in the published paper.

Expert clinicians in this context were defined as senior consultant level doctors with specialty qualifications in either General Paediatrics or Paediatric Emergency Medicine.

Model parameters were considered to have face-validity if 80% of the surveyed experts considered each individual data point to be an acceptable and plausible reflection of their observed local practice.

The survey was a written survey administered either face-to-face or by telephone (Appendix 11.4.1). The doctoral candidate administered all 20 surveys.

6.7.7 Assumptions

Some assumptions were required to complete the model. Clinical practice involves an inherent amount of variability, but it is not possible to capture all of this variability within a decision analytic model.

Assumptions used were proposed by the doctoral candidate, and followed usual local clinical practice as closely as possible. The assumptions were then

refined according to consensus from the study team, and are described in the published paper.

6.7.8 Completion of the model

The collected costs and probabilities data were recorded by the doctoral candidate in a Microsoft Excel spreadsheet, and then entered into the TreeAge Pro database.

6.7.9 Costs and cost-effectiveness analyses

Costs analyses for the average costs of collection by each method were performed using TreeAge Pro.

Cost-effectiveness analysis was performed for Phase 1 which is the initial collection attempt. It was assumed in the model that if the initial collection attempt was unsuccessful, that subsequent collection by catheterisation would be 100% successful, and so for Phases 2 and 3 of the model, all collection had 100% effectiveness. Therefore it was possible to compare average costs for all phases of the model, but compare cost-effectiveness only for Phase 1 of the model.

All analyses were performed by the doctoral candidate, with supervision from health economists Dr Knight and A/Prof Dalziel.

6.7.10 Sensitivity analyses

Measures of costs, outcomes and effectiveness used in economic evaluations may be based on certain assumptions, and therefore include a degree of uncertainty.

The sensitivity analysis can be used to determine the degree of uncertainty around estimations of cost-effectiveness. Cost and effectiveness inputs can be varied to reflect other plausible circumstances. Sensitivity analyses can be

one-way (to determine the single greatest source of uncertainty), multi-way (to determine the combined impact of a few main drivers of uncertainty) or probabilistic (to simulate the combined impact of all parameter uncertainty). [256] The uncertainty can be represented with confidence intervals for the estimated cost-effectiveness.

One-way and probabilistic sensitivity analyses were performed as described in the published paper for the Phase 3 average costs for each method, with further detail and rationale described below.

6.7.10.1 One-way sensitivity analyses

One-way sensitivity analyses vary a parameter estimate independently to determine the impact on model results. [257] These were performed for key variables and assumptions thought likely to have the greatest impact on the model, which were selected a priori. The rationale for each variable or assumption selected is described in this section.

Costs for staff, equipment and hospital bed occupancy could vary between settings. These costs were therefore each independently increased and decreased by 20% for the sensitivity analysis, as a plausible estimate of general cost variation.

It was assumed for the model that non-invasive collection was performed by nursing staff. However if non-invasive collection was performed by doctors, this could increase the staff costs for the procedure. Therefore the sensitivity analysis included having non-invasive collection performed by doctors rather than nurses.

It was assumed for the model that invasive collection was performed by senior trainee doctors, as departmental staffing in Australian ED settings generally includes a much higher proportion of trainee doctors than consultant level doctors. However consultant level doctors also perform these procedures, and their staff costs are substantially higher. Therefore the sensitivity analysis included having all procedures performed by a consultant level doctor.

The one-way sensitivity analyses also included survey counter-factuals. A counter-factual is a state contrary to the known facts. In this economic evaluation a counter-factual analysis was performed where <80% of surveyed expert clinicians considered that the data point obtained from the literature plausibly reflected their local practice. The counter-factual analysis used the mean value from the survey estimates for that data point. This occurred for 3 out of 25 data points in the model.

6.7.10.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses assess the joint uncertainty across all parameters in the model simultaneously, where correlation between parameters exists. [257] Model parameter values are sampled from the distributions of variables in the model. If the data used for the model includes only a small sample of values, such as small sample sizes for studies in the literature, greater uncertainty around the results of the model is expected.

The sample sizes and standard deviations of model parameters are reported in Table 1 of the published paper. Where the standard deviation of model parameters was not directly reported, the doctoral candidate calculated the standard deviation from the published data, or where this was not possible the standard deviation was estimated using the Briggs Assumption. [265] Distributions for each parameter were chosen to reflect the nature of the data. [257]

Monte Carlo simulations use repeated random sampling from designated parameter distributions. [257] The model is run repeatedly for combinations of parameter estimates, which then estimates 95% confidence intervals around model results. [257] In this economic evaluation, one thousand simulations were performed for each method.

6.8 RESULTS

The results of the Liquid Gold health economic evaluation are described in this section. This includes the published results paper, as well as further detail

and elaboration not included in the published paper which contribute to the interpretation and discussion of the results.

6.8.1 Published results paper (Paper 5)

The results of the analysis are published in the journal *Archives of Disease in Childhood*, and the published paper is included below:

Liquid gold: the cost-effectiveness of urine sample collection methods for young precontinent children

Jonathan Kaufman,[1,2,3] Andrew Joshua Knight,[4] Penelope A Bryant,[1,2,3] Franz E Babl,[1,2,3] Kim Dalziel[3,4]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2019-317561).

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ABSTRACT

Background Urinary tract infection (UTI) is a common childhood infection. Many febrile children require a urine sample to diagnose or exclude UTI. Collecting urine from young children can be time-consuming, unsuccessful or contaminated. Cost-effectiveness of each collection method in the emergency department is unknown.

Objective To determine the cost-effectiveness of urine collection methods for precontinent children.

Methods A cost-effectiveness analysis was conducted comparing non-invasive (urine bag, clean catch and 5 min voiding stimulation for clean catch) and invasive (catheterisation and suprapubic aspirate (SPA)) collection methods, for children aged 0–24 months in the emergency department. Costs included equipment, staff time and hospital bed occupancy. If initial collection attempts were unsuccessful subsequent collection using catheterisation was assumed. The final outcome was a definitive sample incorporating progressive dipstick, culture and contamination results. Average costs and outcomes were calculated for initial collection attempts and obtaining a definitive sample. One-way and probabilistic sensitivity analyses were performed.

Results For initial collection attempts, catheterisation had the lowest cost per successful collection (GBP£25.98) compared with SPA (£37.80), voiding stimulation (£41.32), clean catch (£52.84) and urine bag (£92.60). For definitive collection, catheterisation had the lowest cost per definitive sample (£49.39) compared with SPA (£51.84), voiding stimulation (£52.25), clean catch (£64.82) and urine bag (£112.28). Time occupying a hospital bed was the most significant determinant of cost.

Conclusion Catheterisation is the most cost-effective urine collection method, and voiding stimulation is the most cost-effective non-invasive method. Urine bags are the most expensive method. Although clinical factors influence choice of method, considering cost-effectiveness for this common procedure has potential for significant aggregate savings.

What is already known on this topic?

- Obtaining a urine sample from young precontinent children can be challenging.
- Samples can be collected using non-invasive (urine bag, clean catch and voiding stimulation for clean catch) or invasive (urethral catheterisation and suprapubic aspirate) methods.
- Collection attempts can be time-consuming or unsuccessful, and samples may be contaminated and therefore not diagnostically conclusive.

What this study adds?

- Catheterisation is the most cost-effective method of urine sample collection from precontinent children.
- Voiding stimulation is the most cost-effective non-invasive method, and urine bags are the most expensive method.
- Time occupying a hospital bed is the most significant determinant of cost.

INTRODUCTION

Urinary tract infection (UTI) is a common infection in early childhood, with a prevalence of 7% among febrile children aged 0–24 months.[1] UTI is the most prevalent bacterial infection in children with fever of unknown origin,[2] but clinical signs in young children are often non-specific. Urine collection is therefore required to diagnose or exclude UTI and is part of the diagnostic work-up for many febrile children in primary care and hospital settings. Collecting urine from young precontinent children can be challenging.

Common collection strategies include non-invasive (urine bag and clean catch) and invasive (catheter and suprapubic aspirate (SPA)) methods (figure 1). Each method has different limitations, clinical practice guidelines have differing recommendations[3–5] and clinicians have different preferences for the preferred method.[6 7] Non-invasive methods can be convenient but are time-consuming and have higher contamination rates.[8] Invasive methods are more reliable, but require expertise and equipment to perform and are painful for the child.[9] Collection success also varies between methods, so multiple attempts may be required to actually collect a sample.[10 11] Recent studies have demonstrated that voiding stimulation techniques performed for 5 min such as bladder–lumbar manoeuvres and the Quick-Wee method can expedite clean catch collection,[12 13] though not all studies are randomised.[14 15]

Difficulties collecting urine samples can be costly and detrimental to patient care. Delayed collection will increase resource use and prolong hospital bed occupancy. Poor quality samples lead to missed diagnoses, unnecessary follow-up and investigations. Misdiagnosis leads to inappropriate antibiotic prescription. Complications and morbidity of

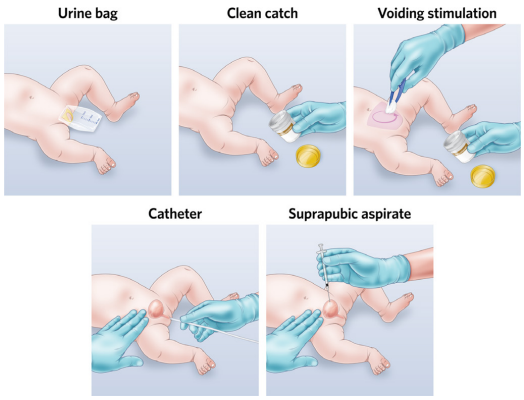


Figure 1 Urine sample collection methods for precontinent children. Images by Dr Jonathan Kaufman and Bill Reid, Royal Children's Hospital. Voiding stimulation figure from Kaufman *et al*.[15]

untreated UTI are uncommon[16 17] but can be significant.[18] It is therefore important to efficiently obtain samples that are likely to be clinically definitive. Initial UTI screening uses bedside dipstick results.[19] However, the gold standard for diagnosis is a positive culture in the presence of pyuria.[20] Sample contamination corrupts these results. Choosing the appropriate collection method balances the clinical context, resource availability, speed, invasiveness, likelihood of success, contamination, parental preferences and costs.

Collection costs are potentially modifiable depending on the method used, but economic evidence regarding collection methods is scarce.[21] Downs estimated urine bags cost an additional US$429 compared with catheterisation, based on unnecessary treatment of false-positive and contaminated samples rather than collection costs.[22] Hollingworth *et al* estimated collection, testing and doctor time in general practice to cost GBP£33, based on clean catch and urine pad collection for children under 5 years in the Diagnosis of Urinary Tract infections in Young children (DUTY) study, not incorporating sample reliability.[23]

Current guideline recommendations for urine collection methods do not incorporate evidence of cost-effectiveness.[20 23] No previous studies directly compare resource use and cost-effectiveness for different collection methods. While costs to collect a single sample may not be high, as a common procedure aggregate costs may be significant.

METHODS

This economic evaluation includes detailed costing and decision analysis of common urine collection methods used for precontinent children in the hospital setting, using an emergency department (ED) health service perspective. The analysis evaluated the costs of sample collection, acknowledging that selecting the appropriate method is influenced by other clinical factors and resource availability. Average and incremental cost-effectiveness estimates are derived for each approach relative to catheterisation.

Diagnostic approaches

These include non-invasive (urine bag, clean catch and 5 min voiding stimulation) and invasive (catheter and SPA) collection methods.

Setting

The population of interest was precontinent children aged 0–24 months requiring urine sample collection in ED to evaluate fever or potential UTI. The Royal Children's Hospital (RCH) is a tertiary paediatric hospital in Melbourne, Australia, with an annual ED census of approximately 90 000 patient contacts.

A probabilistic decision analytic model was constructed using TreeAgePro 2017.[24] The model consists of three stages of attempting and collecting a urine sample and then reaching a definitive decision to exclude or diagnose UTI (figure 2). The three-stage modelling for each method is summarised as:

1. Choice of urine collection method (first collection attempt).
2. Urine collection success (if first attempt unsuccessful, then sample collected by catheterisation).
3. Definitive UTI diagnosis (incorporating dipstick, culture and contamination results).

All children progress through the model until a urine sample is collected and sufficient information is available to reach a conclusive decision regarding UTI diagnosis. Cost-effectiveness is presented for stage 1 of the model only, as subsequent collection by catheter in stages 2 and 3 was assumed to be 100% effective after unsuccessful initial attempts. Further costs were added for stages 2 and 3.

Model parameters

Best estimates for model values and probabilities were obtained from a review of the published literature (table 1). Where multiple data were available, larger studies or those most reflecting the research setting were prioritised.

Outcome assumptions

Some assumptions were required to complete the modelling, and these were based on usual local practice. We assumed non-invasive collection was performed by nurses, and invasive collection was performed by senior trainee level doctors with nursing staff assistance. Urine collection pads are not used in our hospital and were not included in the model. We assumed ultrasound guidance was not used. We assumed after failed initial collection attempts clinicians would go directly to successful catheterisation, consistent with the reported 100% success of catheterisation after failed SPA in previous studies.[25] We assumed bedside dipstick testing was performed on all samples, with a binary positive/negative result, with all positive dipsticks sent for culture and some negative dipsticks sent for culture depending on collection method (table 1). We assumed cultures had a binary positive/negative or contaminated result, where contamination was heavy mixed growth and an uninterpretable outcome. We assumed consultant level doctors reviewed culture results, and if patients with contaminated samples were recalled that subsequent catheterisation would be successful and definitive.

Resource use and costs

Resource use was determined using prospective process mapping, directly observing 10 episodes of each collection method, to identify equipment use and staff time (nursing and medical) for each method. Mean equipment and staff costs for each method were calculated from these data (online supplementary appendix 2). Costs are presented in 2016 GBP£ (equivalent to $A2.08) using the 2016 Purchasing Power Parity from the Organisation for Economic Co-operation and Development Statistics (table 2).

We assumed standardised cleaning used one dressing pack and chlorhexidine ampoule. We assumed dipstick testing required equipment plus 3 min nursing time (£0.98), and culture testing

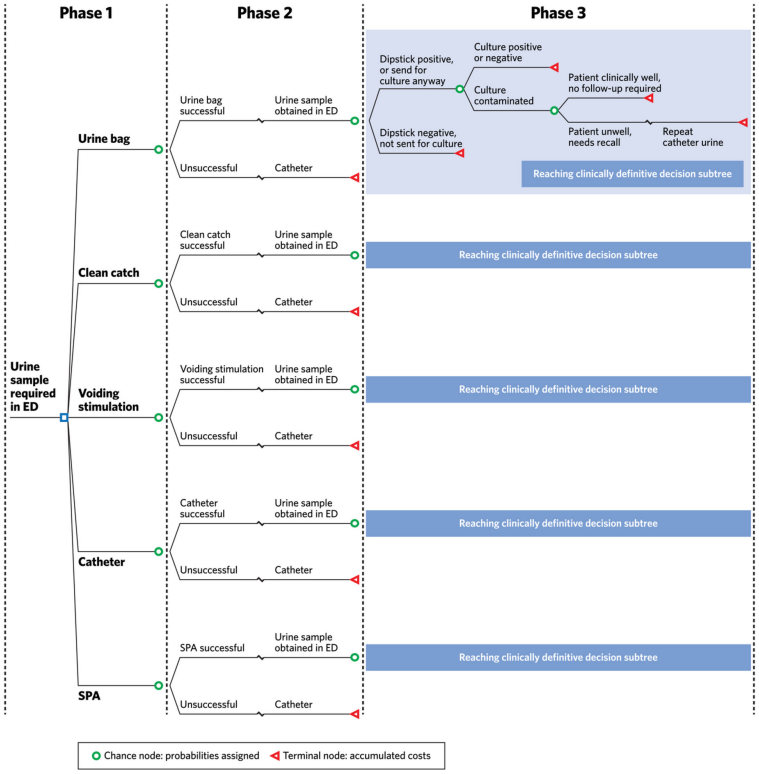


Figure 2 Decision tree for urine sample collection and UTI diagnosis. ED, emergency department; SPA, suprapubic aspirate.

required laboratory costs (which already incorporate microbiology scientist and clinician time) plus 6 min consultant doctor time checking results and contacting some families to revise prescriptions or recall patients with contaminated specimens if they remained unwell (£18.61), consistent with previous studies.[23] For patients requiring recall, we assumed another 30 min ED presentation with repeat catheter urine collection plus dipstick and culture to clarify the diagnosis (£73.30). We observed all collection methods except urine bag, which is not routinely performed in our ED. We therefore assumed standard cleaning plus one urine bag and 5 min of nursing time was required for bag collection attempts.

Model validation using clinician survey

We surveyed 20 senior clinicians (consultant paediatricians and paediatric emergency physicians, mean 17 years clinical experience) to determine the face validity of the model and elicit expert opinion for probabilities not available from the literature (online supplementary appendix 1).

We first asked clinicians to estimate critical values used in the model for each collection method (table 1) including time, collection success, contamination, likelihood samples would be sent for laboratory processing after dipstick testing, and likelihood patients would be recalled for review if samples were contaminated.

We then revealed the values obtained from the literature review and asked the clinician if each data point was acceptable and plausibly reflected their local departmental practice. Where <80% of clinicians felt the data plausibly reflected local practice, we performed counterfactual scenario analyses using the mean clinicians' estimate to determine the importance of that variable.

Analysis

Data from survey and process mapping forms was entered into Microsoft Excel (2017). Costs and probabilities were then assigned to the decision tree model in TreeAgePro (2017).[24] The study followed the Consolidated Health Economic Evaluation Reporting Standards reporting guidelines.[26]

Sensitivity analysis

To determine the robustness of model assumptions, and describe the impact of uncertainty in parameter values, we performed sensitivity analyses for the complete model (stage 3). One-way sensitivity analyses were performed on the following key variables and assumptions (online supplementary appendix 1):

- Staff, equipment and hospital bed costs each increased and decreased ±20%.
- Non-invasive collection procedures performed by doctors rather than nurses.
- All procedures performed by senior doctor (consultant level).

One-way analyses based on survey counterfactuals were also performed (appendices 1 and 3):

- Urine bag effectiveness decreased from 96% to 67%.

Table 1 Model inputs: time, success and urine test results

Parameter	Estimate (mean)	Number of data estimate derived from (N)	SD	Distribution	Source
Urine bag					
Procedure time	85 min	23	67 min	Log normal	McKune[35]
Success	96%	169	48%*	Beta	Alam *et al*[36]
Contamination	46%	13	23%*	Beta	Tosif *et al*[8]
Send sample for culture	72%	504	36%*	Beta	Schroeder *et al*[37]
Recall patient if culture contaminated	33%	20	23%	Beta	Expert opinion†
Clean catch					
Procedure time	31 min	218	42 min	Log normal	Tosif *et al*[11]
Success	64%	218	45%	Beta	Tosif *et al*[11]
Contamination	26%	202	13%*	Beta	Tosif *et al*[8]
Send sample for culture	80%	160	40%*	Beta	Tosif *et al*[11]
Recall patient if culture contaminated	40%	20	25%	Beta	Expert opinion†
Voiding stimulation (Quick-Wee method)					
Procedure time	5 min	N/A‡	N/A‡	Fixed	Kaufman *et al*[15]
Success	30%	174	47%	Beta	Kaufman *et al*[15]
Contamination	27%	44	47%	Beta	Kaufman *et al*[15]
Send sample for culture	85%	52	42%*	Beta	Kaufman *et al*[15]
Recall patient if culture contaminated	37%	20	20%	Beta	Expert opinion†
Catheter					
Procedure time	12 min	45	7 min	Log normal	Baumann *et al*[38]
Success	90%	148	45%*	Beta	Poonai 2015[39]¶¶
Contamination	12%	97	6%*	Beta	Tosif *et al*[8]
Send sample for culture	95%	1030	47%*	Beta	Schroeder *et al*[37]
Recall patient if culture contaminated	60%	20	23%	Beta	Expert opinion†
Suprapubic aspirate					
Procedure time	8 min	20	4 min	Log normal	Expert opinion†
Success	44%	38	22%*	Beta	Munir *et al*[10]
Contamination	1%	84	0.05%*	Beta	Tosif *et al*[8]
Send sample for culture	100%	N/A¶	N/A§¶	Fixed	RCH[5]
Recall patient if culture contaminated	72%	20	26%	Beta	Expert opinion†

Procedure time: from starting collection process to when urine voided or collection attempt stopped.
¶¶Personal correspondence with author to clarify data.
*SD or data distribution not available; SD estimated using Briggs assumption.[40]
†Where published data were unavailable, we used expert opinion from surveying 20 senior paediatricians and paediatric emergency physicians.
‡Assumed fixed 5 min duration for all voiding stimulation attempts.
§Personal correspondence with author to clarify data.
¶Based on Clinical Practice Guideline recommendation.
RCH, Royal Children's Hospital.

- Probability of bag samples sent to laboratory where dipstick negative reduced from 72% to 48%.
- Clean catch time increased from 31 min to 83 min.

We considered any factor affecting the hierarchy of results or shifting final results by >25% to be meaningful.

Probabilistic sensitivity analysis was performed to examine the impact of the joint uncertainty of the model parameters. One thousand simulations were performed using Monte Carlo sampling to randomly sample from relevant parameter distributions (online supplementary appendix 3).

RESULTS

For initial collection attempts, catheterisation had the most favourable average cost-effectiveness with a cost per successful collection of £25.98, and for non-invasive methods voiding stimulation had the most favourable cost-effectiveness with cost per successful collection of £41.32 (table 3).

To obtain definitive samples, catheterisation had the lowest average cost per definitive sample obtained (£49.39) and for non-invasive methods voiding stimulation had the lowest cost per definitive sample obtained (£52.25) (table 3).

Sensitivity analysis

The results of one-way sensitivity analyses of key variables are presented in online supplementary appendix 3. These analyses did not alter the hierarchy of model conclusions, indicating results were robust to changes in key parameters. Having consultant level doctors perform all procedures had the greatest impact, increasing costs by 6%–21% depending on method.

One-way analyses based on survey counterfactuals were also performed (online supplementary appendices 1 and 3). Increasing clean catch time by 170% increased the cost of collecting a definitive sample by clean catch from £64.82 to £118.15, indicating that time occupying a hospital bed is a significant driver of collection costs. Other counterfactuals did not substantially affect conclusions.

When simulated 1000 times, the average costs per definitive sample obtained were £48.60 catheterisation (95% CI £33.54

Table 2 Costs used in economic model

Unit prices per unit of care			
Item	**Unit cost (GBP)**	**Distribution**	**Source**
Equipment			
Cleaning fluid (clorhexidine)	0.76	Fixed	RCH Procurement
Dressing pack	0.2	Fixed	RCH Procurement
Gauze pack	0.09	Fixed	RCH Procurement
Specimen jar	0.05	Fixed	RCH Procurement
Syringe	0.02	Fixed	RCH Procurement
Urine bag	0.43	Fixed	RCH Procurement
Saline ampoule	0.04	Fixed	RCH Pharmacy
Bluey	0.06	Fixed	RCH Procurement
Lubricant sachet	0.31	Fixed	RCH Procurement
Catheter tube	0.14	Fixed	RCH Procurement
Needle and syringe	0.03	Fixed	RCH Procurement
Sterile gloves	0.67	Fixed	RCH Procurement
Non-sterile gloves	0.03	Fixed	RCH Procurement
Specimen bag	0.02	Fixed	RCH Procurement
Tests			
Dipstick	0.07	Fixed	RCH Procurement
Laboratory culture	9.89	Fixed	Medicare benefits scheme

Costs related to time per test			
Item	**Value (GBP) (mean)**	**Distribution**	**Source**
Staff*			
ED nurse	18.26/hour	Min 16.96/hour, max 30.89/hour	Victorian Public Sector Nursing Award 2016–2020†
ED senior trainee doctor	27.45/hour	Min 19.95/hour, max 37.19/hour	AMA Victoria Doctor In Training Award 2013–2017†
ED consultant doctor	87.07/hour	Min 73.56/hour, max 95.87/hour	AMA Victoria Medical Specialists Award 2013–2017†
Hospital			
ED bed (total cost per presentation)	60.66/hour	95% CI 8.09 to 121.31/hour	Department of Health & Human Services, RCH average cost 2015/2016

*Mean staff level based on estimate of RN grade 2 year 3 nurse, registrar year 3 doctor, specialist year 5 senior doctor.
†Base salary plus 23.62% hospital on-costs.
AMA, Australian Medical Association; ED, emergency department; RCH, Royal Children's Hospital.

to £131.71), $50.67 SPA (95% CI £39.72 to £97.93), £51.21 voiding stimulation (95% CI £40.97 to £105.95), £65.03 clean catch (95% CI £30.27 to £313.48) and £126.43 urine bag (£59.92 to £323.38). Uncertainty in these results reflects some variability in the published data used to inform the model (table 1).

DISCUSSION

Summary of findings

This study evaluated the cost-effectiveness of urine sample collection from an ED healthcare system perspective. Invasive methods were more cost-effective than non-invasive methods although with some simulated uncertainty. Catheterisation was the most cost-effective approach to obtain both initial and definitive samples. Catheterisation is highly effective, with moderate procedural costs and low contamination.[8] SPA has even lower procedural costs and ultra-low contamination[8] but is less effective at obtaining a sample.[25] These invasive methods require equipment and technical expertise to perform. Resource availability and clinician experience may limit their utilisation in some settings. Use of invasive methods is also strongly influenced by clinical factors, discomfort caused to the child and parental preferences.[9 27 28] Usual care will vary according to these factors, though in some settings urethral catherisation or suprapubic aspiration is already the dominant practice.[20] Quality of life was not included in this study, but children's pain and parents distress are important considerations.[29]

For non-invasive collection, voiding stimulation was the most cost-effective approach to obtain both initial and definitive samples. It is less effective but uses a shorter timeframe when performed for the recommended 5 min. We modelled voiding stimulation based on the published Quick-Wee method,[13] as bladder–lumbar manoeuvres require multiple operators, and there are no randomised studies in the ED setting.[12] Urine bags were the most expensive method for all stages of the model, reflecting their time-consuming nature and that high contamination means that samples are often not definitive.

Time spent occupying a hospital bed was the most significant determinant of collection cost. Therefore, expedient methods performed more favourably from this study's costs perspective. Sample contamination also contributes to cost-effectiveness but was not the major determinant in the hospital setting. However, in the general practice context where parents may collect urine samples at home, contamination is likely to be a much greater determinant of costs.

The 2016 RCH costing data showed non-admitted UTI patients aged <24 months had a mean time in ED of 240 min, with 156 min occupying an ED cubicle, with a cost of £211.34 per episode. National data showed average costs for UTI patients aged <24 months of £261.40 per non-admitted ED episode.[30]

Table 3 Average costs and incremental cost-effectiveness of urine sample collection

Stage 1: first collection attempt

Collection method	Cost (GBP)	Incremental cost versus control (catheter) (GBP)	Effectiveness	Incremental effectiveness	ICER (GBP)	Average cost-effectiveness (cost per successful collection by designated method) (GBP)
Catheter	23.38		0.9			25.98
SPA	16.63	−6.75	0.44	−0.46	14.67	37.80
Voiding stimulation	12.40	−10.98	0.3	−0.6	18.30	41.32
Clean catch	33.81	10.43	0.64	−0.26	Dominated *	52.84
Urine bag	88.90	65.52	0.96	0.06	1091.98	92.60

Stage 2: sample collected by catheterisation if initial attempt unsuccessful

Initial collection method	Cost (GBP)	Incremental cost per successful sample obtained versus control (GBP)
Catheter	25.72	
SPA	28.76	3.05
Voiding stimulation	29.72	4.01
Clean catch	42.23	16.51
Urine bag	89.83	64.11

Stage 3:obtaining an ultimately definitive sample

Initial collection method	Cost (GBP)	Incremental cost per definitive sample obtained versus control (GBP)
Catheter	49.39	
SPA	51.84	2.45
Voiding stimulation	52.25	2.86
Clean catch	64.82	15.43
Urine bag	112.28	62.89

*Dominated refers to an intervention that is more costly and also less effective than the comparator.
ICER, incremental cost-effectiveness ratio; SPA, suprapubic aspirate.

Urine sample collection therefore accounts for approximately 20%–50% of these costs, depending on collection method.

While ultrasound evaluation of bladder volume can increase the success of invasive collection attempts,[31 32] its use is not routine for non-invasive collection, and the required equipment and expertise is not universally available.

Strengths and limitations

This is the first study directly comparing cost-effectiveness of urine sample collection by collection method. Model inputs were based on comprehensive data from the published literature, prospective process mapping and survey of expert clinicians. This is the first study to include all costs of collecting a sample, and the pragmatic considerations of progressively available dipstick and laboratory results used to reach a clinically definitive decision.

We made certain model assumptions, including that if the first collection attempt was unsuccessful, the clinician would proceed to catheterisation. This may not reflect all clinical scenarios but was a necessary simplification. We assumed non-invasive collection was performed by nurses and invasive collection performed by doctors; however, in some settings, non-invasive collection may be performed by doctors and vice versa. In sensitivity analyses, having all procedures performed by doctors did not change model conclusions. Our study was conducted in a tertiary paediatric ED. Results will not be directly generalisable to non-hospital settings such as general practice.

We did not include parental costs such as travel and time off work, although these would likely strengthen conclusions given parental costs likely reflect time taken. Quality of life was not included, but children's pain and parents' distress are important considerations.[28 29]

Clinical implications

Urine sample collection from young children is common in paediatrics, general practice and emergency medicine. Our findings provide new cost-effectiveness data to inform future guideline recommendations. Where invasive collection is indicated, these methods are cost-effective.

Where non-invasive collection is indicated, voiding stimulation methods are cost-effective and also expedite patient care. UK and European guidelines recommend clean catch as the preferred method of urine sample collection,[4 33] although urine bag collection is frequently performed.[34] In 2016, in our local setting at the RCH ED, 1776 urine samples from children aged 0–24 months were sent for laboratory processing from 87797 patient presentations from all ages. This represents collecting urine for culture from a young precontinent child in 2% of all paediatric ED presentations. Samples were collected by clean catch (78%), catheter (11%), SPA (7%) or method unstated (4%). Using voiding stimulation in preference to standard clean catch in the ED could save £12.57 per sample and over £17000 annually.

CONCLUSION

From a healthcare system costs perspective, the most cost-effective invasive and non-invasive urine collection methods are catheterisation and voiding stimulation, respectively. Urine bags are the most expensive method. Time spent occupying a hospital bed

was the most significant determinant of cost. While clinical and patient factors strongly influence the choice of urine collection method, considering cost-effectiveness for this common paediatric procedure has the potential for significant cost savings.

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Contributors JK was the lead author of the manuscript. All authors contributed to the initial study design. JK completed the literature review and acquired all data for the clinician survey, process mapping and cost analysis. JK designed the economic model and completed the analysis with substantial input from AK and KD who supervised the modelling and interpretation of results. PAB and FEB contributed to clinical aspects of the model. JK wrote the first draft of the manuscript, and all authors contributed to revising the manuscript. All authors had final approval of the version to be published. JK and KD take responsibility for the paper as a whole.

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6.8.2 Results in Australian dollars

Costs were converted to British pounds (£GBP) as described in the published paper, for publication in the UK journal *Archives of Disease in Childhood*. Results for costs and cost-effectiveness to obtain an ultimately definitive sample (Phase 3 of the model) from Table 3 in the published paper are presented here with the original $AUD values (Table 6).

Table 6: Costs of obtaining an ultimately definitive sample

Initial Collection Method	Average cost	Incremental cost per successful sample obtained vs control
Catheter (control)	$102.60	
SPA	$107.68	$5.07
Voiding stimulation	$108.53	$5.92
Clean catch	$134.64	$32.03
Urine bag	$233.23	$130.62

6.9 RESULTS IN CONTEXT

Data from the published economic evaluation demonstrated the costs to collect a definitive urine sample for an individual patient.

The total cost burden and potential cost savings at scale were subsequently estimated, to provide a context for the published results of individual collection costs, for:

1. Hospital level savings (RCH): ED and whole of hospital
2. National level savings (Australia): ED and whole of hospital

Additional data regarding hospital presentations requiring urine sample collection was used to estimate the total cost burden of urine sample collection. This included the local data obtained from the RCH Decision Support Unit and RCH Pathology Department, and national data obtained from IHPA and Medicare, as described in the methods section of this chapter. Relevant data is summarized in this section and further detail and additional data is available in Appendix 11.7.1.

Cost savings from using optimal collection methods were estimated for changes between non-invasive collection methods. Changing from clean catch to the Quick-Wee method is a simple practice change. Published data supports that this change would be acceptable to clinicians and parents. [251] Changing from urine bags to the Quick-Wee method would also likely be acceptable to clinicians and families.

Cost savings were not estimated for changes from non-invasive to invasive collection methods, as it was felt less likely that widespread practice change favouring use of invasive collection methods would occur on the basis of economic data alone.

6.9.1 Local costs and cost savings: ED

As described previously, the RCH ED is a tertiary paediatric ED in Melbourne, Australia. In 2016 the RCH ED had an annual census of 87797 children of all ages, of which 29481 were aged 0-24 months.

1776 urine samples were sent for laboratory culture from children aged 0-24 months in the ED for laboratory culture in 2016, not including additional samples collected for dipstick screening only. This represents collecting a urine sample for culture from 6% of all paediatric ED presentations in this age group. Following local guidelines, most samples (78%) were collected using the clean catch method (see Table 7).

Collecting urine samples for culture from young pre-continent children in the RCH ED has an estimated annual total cost of over $200000 (Table 7). Further samples collected for dipstick screening only are not included in this cost estimate.

Table 7: Collection methods and costs in the RCH ED

RCH ED only, children aged 0-24 months (2016)			
Collection method	**Number (%)**	**Cost per sample**	**Estimated total cost by method**
Bag	9 (<1%)	$233.23	$2099
Clean Catch	1384 (78%)	$134.64	$186342
Catheter	200 (11%)	$102.60	$20520
SPA	122 (7%)	$107.68	$13137
Unstated/other	61 (4%)	-	-
Total (all methods)	1776		$222098

Assumed if documented as "midstream" from child 0-24 months this was a clean-catch collection from a pre-continent child

Other: e.g mitrofanoff or ureterostomy sample

Total cost estimate does not include 61 samples collected by unstated/other methods.

The economic evaluation demonstrated that collecting a definitive urine sample using the Quick-Wee method is $26.10 cheaper than collection with standard clean catch. Collection of 1384 clean catch samples for culture in 2016 had an estimated cost of $186342. Collecting these samples using the Quick-Wee method would have an estimated cost of $150206, representing a potential annual cost saving of $36136.

However modelling in the published economic evaluation specifically considered samples that were collected for dipstick but not sent for culture (see Table 1 and Figure 2 of published paper), and included these probabilities and costs in calculating average collection costs. For that reason, estimates of total departmental annual cost savings should include these additional samples that were not sent for culture. For clean catch collection, the preceding baseline study showed that only 80% of clean catch samples were sent for culture. [244]

Including the additional 20% of clean catch samples collected for dipstick only, **estimated annual cost savings in the RCH ED from using the Quick-Wee method in favour of standard clean catch would be $43363.**

6.9.2 Local costs and cost savings: hospital wide

The RCH is a tertiary paediatric hospital with approximately 350 beds. In 2016 the hospital had 48552 admissions.

3225 urine samples from children in this age group were sent for laboratory culture hospital wide in 2016 (Table 8). This included 1776 samples from the ED (55%) and 1449 from hospital wards (45%) (Table 17, Appendix 11.7.1). This represents a total of 62 urine cultures hospital wide per week for children in this age group.

Collecting urine samples from young pre-continent children hospital wide at RCH in 2016 had an estimated annual total cost of over $350000 (Table 8).

1924 clean catches were collected hospital wide in 2016, at an estimated cost of $259047. Collecting these samples using the Quick-Wee method would have an estimated cost of $208811, representing a potential annual cost saving of $50236.

Table 8: Collection methods and costs in the RCH hospital wide

RCH Hospital Wide (ED and wards), children aged 0-24 months (2016)			
Collection method	**Number (%)**	**Cost per sample**	**Estimated total cost by method**
Bag	31 (1%)	$233.23	$7230
Clean catch	1924 (60%)	$134.64	$259047
Catheter	689 (21%)	$102.60	$70691
SPA	190 (6%)	$107.68	$20459
Unstated/other	391 (12%)	-	-
Total (all methods)	3225		$357427

Assumed if documented as "midstream" from child 0-24 months this was a clean-catch collection from a pre-continent child

Other: e.g mitrofanoff or ureterostomy sample

Total cost estimate does not include 391 samples collected by unstated/other methods.

As described previously, including an additional 20% of samples collected for dipstick screening but not sent for culture, **this represents the estimated annual cost savings at RCH hospital wide from using the Quick-Wee method in favour of standard clean catch would be $60283**.

6.9.2.1 Correlation between ICD-10 codes for UTI and unexplained fever, and laboratory data for urine cultures, for number of urine samples collected

Hospital wide in 2016, ICD-10 coded data from the RCH Decision Support Unit showed there were a total of 340 patients aged 0-24 months with a primary diagnosis of UTI, and 612 patients with a primary diagnosis of unexplained fever patients (Appendix 11.7.1, Table 16). At face value it would

be assumed that most children who need a urine sample collected would have a main diagnosis of either UTI or unexplained fever.

For the same time period, RCH laboratory data showed that 3225 urine samples were actually sent for laboratory culture from children in this age group (Appendix 11.7.1, Table 17). This suggests that using ICD-10 diagnostic codes for UTI and unexplained fever significantly underestimates the total number of urine samples collected in the hospital. This poor correlation has important implications for scaling up cost estimates to a national scale, as described subsequently.

6.9.3 National costs and cost savings: ED

Estimated costs of urine sample collection from young children in EDs nationally can be extrapolated and scaled up from RCH data.

Australian government hospital statistics show that in the 2015-16 financial year there were 854459 hospital ED presentations for children 0-4yo. [266] Assuming half of these were children aged 0-2yo, this equates to 427229 young pre-continent children (specific data for this age group was not available).

Extrapolating from the RCH ED data presented in section 6.9.1 that 6% of all ED presentations from children aged 0-24 months include having a urine sample sent for culture, this would equate to 25634 samples from this age group in Australian EDs annually. Including an additional 20% of samples collected for dipstick only, this would equate to 30761 samples.

Clean catch is the recommended first line collection method in Australian guidelines, and is used for 78% of samples collected in the RCH ED (Table 7). Extrapolating to the national estimate of 30761 samples from all collection methods, this would equate to 23994 clean catch samples, which at a cost of $134.64 per sample would cost $3230552. Collecting these samples using the Quick-Wee method would cost $2604069.

This represents an estimated annual cost saving in Australian EDs from using the Quick-Wee method in favour of standard clean catch of $626483.

6.9.4 National costs and cost savings: hospital wide

Estimated costs of urine sample collection from young children in hospitals nationally can also be extrapolated from RCH data.

Initially, national IHPA data was obtained to estimate how many young children presenting to hospital in Australia require urine sample collection annually. The IHPA data showed that in the 2015/16 financial year, 28269 children aged 0-24 months had both admitted and non-admitted episodes with ICD-10 diagnostic codes for UTI and unexplained fever (Appendix 11.7.1, Tables 18-19). Given the estimate that over 30000 samples are collected in ED alone, this data seems to significantly underestimate the total number of urine samples collected hospital wide. Local RCH data for 2016 is consistent with this observation, where 952 patients at RCH had ICD-10 codes for UTI or unexplained fever (Appendix 11.7.1, Table 16), but 3225 urine samples were actually sent to the laboratory (Appendix 11.7.1, Table 17).

Therefore national hospital wide costs were estimated by extrapolating amd scaling up from ED and RCH data. From an estimated 30761 samples collected in EDs nationally, and from RCH proportions that from all samples 55% are collected in ED and 45% from hospital wards (Table 17, Appendix 11.7.1), an additional 25168 samples would be collected from hospital wards nationally, for a total of 55929 samples hospital wide from all Australian hospitals. Based on RCH proportions of 60% samples hospital wide being collected by clean catch (Table 8), an estimated 33557 clean catch samples would be collected hospital wide nationally. At a cost of $134.64 per clean catch sample, annual Australian hospital costs for clean catch collection would be $4518114. Collecting these samples using the Quick-Wee method at a cost of $108.53 per sample would cost $3641941.

This represents an estimated annual cost saving in Australian hospitals from using the Quick-Wee method in favour of standard clean catch of $876173.

In reality, it is likely that a moderate proportion of bag specimens are collected in hospitals in Australia, particularly outside of tertiary centres. Published data suggests bag collection is used in Australian hospitals for up to 25% of urine samples for children aged 0-24 months. [142] If 25% of the 55929 samples collected nationally used the urine bag method, this equates to 13982 urine bag samples. The Quick-Wee collection method costs $108.53, which is substantially cheaper than urine bag collection which costs $233.23.

Using the Quick-Wee method in favour of urine bags at this scale would provide an estimated cost saving of an additional $1743555.

6.9.5 Primary care costs and cost savings

In 2016, data obtained from Medicare showed that 46524 children aged 0-24 months had an MBS service for item urine culture laboratory processing. [267]

However this economic evaluation adopted a hospital costs perspective. Therefore although costs savings from choosing cost-effective sample collection methods would be expected in the primary care setting, exact costs data and results from this economic evaluation cannot be directly applied to a primary care context.

6.10 DISCUSSION

This discussion considers the strengths and limitations of the economic evaluation methods, data sources used, the significance of the research and implications for practice.

6.10.1 Research in context of other published studies.

This economic evaluation is the first to comprehensively evaluate and compare the costs and cost-effectiveness of urine sample collection methods used for young pre-continent children.

As identified in the targeted literature review in section 6.4, few previous studies have reported or estimated these costs, and only one measured any of the actual costs of urine sample collection. The 2016 DUTY study, as part of a comprehensive and broader economic evaluation, estimated the time in the UK primary care setting to attempt collection of a urine sample, dipstick test, interpret culture results and contact parents to revise prescriptions to be 17 minutes and 45 seconds, at a cost of £27.32, plus an additional £6.75 for the dipstick and laboratory testing. [31] Time taken for sample collection was based on time and motion observations for urine sample collection using nappy pads or clean catch for 6 patients, and the study included older continent children up to the age of 5 years. Time taken for GP interpretation and follow-up of results was based on expert opinion. [31]

The Liquid Gold economic evaluation is therefore the first to use comprehensive data from the literature and prospective process mapping from a real-world setting to calculate and compare the actual costs of urine sample collection, for both non-invasive and invasive collection methods.

6.10.2 Strengths and limitations

Strengths and limitations of the model are described briefly in the published manuscript, and explored further in this section. Study methods were robust and followed the recommended CHEERS reporting guidelines. [258]

Considering common and recommended appraisal items for economic evaluations, [268] this study has a number of methodological strengths that suggest results are valid and important, and like any study, has some limitations.

6.10.2.1 Validity of results: strengths

The economic evaluation posed a well defined question, adopting an appropriate hospital costs perspective. All urine sample collection methods commonly used in this setting were considered.

Relevant probabilities and costs were considered over a clinically relevant time horizon, informed by published and prospectively collected data, and displayed clearly in the model decision tree.

A survey of expert clinicians verified the face validity of the model and of the data used to inform model probabilities.

6.10.2.2 Validity of results: limitations

The evaluation could have considered urine pads, which is mentioned as an acceptable collection method in UK guidelines. [186] However pads are not commonly used in the hospital setting, and are not used at all in our local setting. Additionally there is limited published data to inform key parameters for urine pads such as time to sample collection, which would create significant uncertainty around these results.

The modelling also assumed that after an initial unsuccessful collection attempt the clinician would proceed directly to catheterisation. This does not reflect all possible variability of real-world practice. For example, after an initial unsuccessful 5 minute voiding stimulation attempt, clinicians may choose to optimise hydration and continue waiting for a clean catch, rather than immediately proceeding with catheterisation. Some parents may refuse invasive collection methods due to the pain and distress caused to the child. In some settings the equipment or expertise required to perform catheterisation may not be available. However as previously stated, this assumption was a necessary simplification to complete the model.

The evaluation could also have considered a longer time horizon and considered further downstream costs associated with UTI misdiagnosis. This includes patient harm from delayed treatment (e.g renal scarring) or

unnecessary investigations and management from misdiagnosis (e.g imaging and specialist follow-up). Previous economic evaluations have considered these longer term costs. [31 255] However an extended time horizon was beyond the scope of this thesis, and would have necessarily included more assumptions where definitive published data was not available, introducing further uncertainty around results. Further, the significance of renal scarring and probability of developing chronic kidney disease and end stage renal failure as a result of childhood UTI, which is a key driver of long term costs, is contested in the literature. [72 97 99 101]

6.10.2.3 Importance of results: strengths

The economic evaluation used data sourced from the best available evidence to inform model probabilities. This included the effectiveness of each collection method, considering both the effectiveness of initial sample collection attempts as well as considering contamination as a crucial factor for reaching a definitive clinical decision.

Costs were measured and valued comprehensively, using realistic costs data derived from appropriate sources. Cost analysis was informed by substantial prospective process mapping for 40 procedures, and considered all relevant staff time, equipment and hospital bed occupancy costs.

Rigorous one-way and probabilistic sensitivity analyses were performed, considering key variables and possible uncertainty in model parameters.

6.10.2.4 Importance of results: limitations

Not all data for model probabilities were based on RCT or systematic review level evidence. However it is common for economic evaluations to integrate the best available evidence from different study designs. For a minority of data points where no published data was available, expert clinical opinion informed the model. This is also common practice in economic evaluations where published data is not available.

Parent and carer costs were not included in the analysis, although these would likely have strengthened model conclusions. Patient quality of life was not included in the analysis, thought this may have reduced the value of invasive collection methods which are known to cause pain and distress.

The probabilistic sensitivity analysis used Monte Carlo sampling to perform 1000 simulations to randomly sample from parameter distributions, generating 95% confidence intervals for collection costs for all methods. These confidence intervals reflect some uncertainty in the published data used to inform the model. As shown in Table 1 of the published paper, some model inputs from the literature were based on small samples with broad data distributions or standard deviation. Further, several parameter values from published studies did not have data distributions available, necessitating use of the Briggs Assumption to estimate standard deviations for 11 of 25 parameters. [265]

6.10.2.5 Generalisability of findings: strengths

These study findings are relevant and generalisable to similar patient populations and similar clinical settings. This may include patient populations of young pre-continent children who require urine sample collection to evaluate potential UTI or unexplained fever.

Findings are likely generalisable across Australian hospitals. The study setting was a paediatric ED at a tertiary public hospital in Australia. State clinical practice guideline recommendations, [16 269] likely staff and resource availability, results of a previously published survey, [142] and results of the clinician survey within this study, all suggest that practice would likely be similar in EDs and paediatric wards in other Australian hospitals.

Findings may also be generalisable to hospitals within healthcare systems that have similar clinical practice, staff training, resource availability and costs to the Australian hospital system. This includes countries such as New Zealand, Canada, Ireland and the UK.

6.10.2.6 Generalisability of findings: limitations

Study findings are not directly generalisable to the primary care setting. This economic evaluation found that time occupying a hospital bed was the most significant driver of costs. In the primary care context, urine sample collection is often performed by parents at home. [136] Staff costs may also differ between specialists and general practitioners.

Costs may also not directly translate to hospital settings in countries where hospital costs for bed occupancy, staff and equipment are substantially more expensive such as America, or substantially cheaper such as in countries with developing economies.

6.10.3 Limitations to extrapolating findings

The results in context section of this chapter provides a “best estimate” of potential hospital level and national level cost savings from introducing the novel Quick-Wee voiding stimulation method into practice. The estimates are based on local data but there is some uncertainty based on assumptions and speculation for national level proportions.

The number of children who require urine sample collection to evaluate potential UTI in the Australian context has not been previously reported. This is difficult to calculate or estimate, due to the health data availability in different Australian contexts. Individual hospital level data is generally available for both diagnostic code and hospital pathology service use. However at a national hospital level, data by diagnostic code is available, but not data for pathology service use. National MBS data captures primary care pathology service use that is funded by the MBS, but this does not include hospital pathology services which in general are not covered by MBS funding, and does not include patient diagnostic codes. These limitations mean it is not possible to collect the same diagnostic and pathology use data across Australian hospitals and primary care settings.

6.10.3.1 Limitations of using ICD-10 diagnostic codes

In Australia, aggregate national level hospital data is captured and reported by patient diagnostic codes such as ICD-10 coding. We have assumed for hospital presentations coded for UTI or unexplained fever that this reflects the need for urine sample collection, and assumed clinicians follow guideline recommendations to collect a urine sample for these indications. But in the real world these diagnostic codes do not always directly correlate with actual urine sample collection, and there are limitations with these data and those assumptions.

Some patients allocated a UTI diagnosis may not actually have a urine sample collected for diagnostic confirmation. A previous US study reported that 32% of children treated for UTI did not have a sample collected for diagnostic confirmation. [124]

Most young children with unexplained fever will have urine sample collection instigated by their treating clinicians, but others may just be observed initially if the child is not too unwell. Australian and UK guidelines allow clinicians wait 24-48 hours before checking a urine sample if the child is not too unwell. [16 186]

Many other patients who have a urine sample collected may have had a different diagnostic code applied to their admission. This includes clinical diagnoses such as sepsis and dehydration, or symptom diagnoses such as vomiting or irritability. In the preceding co-authored baseline study, 59% of young children had unexplained fever as the primary clinical indication for collecting a urine sample, 13% had suspected UTI, but 38% had other reasons such as vomiting, irritability and poor oral intake. [244] In the Quick-Wee RCT, only 58% of the 344 infants had suspected UTI or unexplained fever reported as a specific indication for urine sample collection in the ED. [251] Many others had urine collected for reasons such as unsettled baby behaviour, poor feeding and vomiting. These indications reflect a possible underlying UTI, but these patients may be assigned other diagnostic codes in the ED. As reported in section 6.9.2.1 the number of patients with diagnostic

codes for UTI and unexplained fever dramatically underestimated the number of patients who actually had a urine sample sent for culture at the RCH.

Therefore ICD-10 diagnostic codes for UTI and unexplained fever could either overestimate or underestimate the number of children who require urine sample collection as part of their hospital presentation. Previous studies have shown that ICD-10 coding can be unreliable for other medical conditions. [270]

6.10.3.2 Limitations of Australian national primary care data

National level primary care data by patient diagnostic code is not available in the Australian context. It was therefore not possible to quantify the number of children presenting to Australian general practices with diagnoses of UTI or unexplained fever. While some data for primary care activity is available from national representative cross-sectional datasets such as the Bettering the Evaluation and Care of Health (BEACH) program, [271] data specific to paediatric UTI and urine sample collection was not available. It was possible to obtain data for the number of Australian patients who have a Medicare Benefits Scheme (MBS) billed urine culture test, but this does not include additional samples collected for dipstick screening but not sent for culture. As the economic evaluation adopted a hospital costs perspective, it was not possible to generalise estimated costs and cost-savings to the primary care setting.

6.10.4 Estimation of cost savings

The cost savings of optimal urine sample collection for initial UTI evaluation were quantified in two ways.

The first was by calculating average costs and cost savings at an individual patient level, and by comparing the costs of different urine sample collection methods. This was the focus of the published economic evaluation, which used robust methodology and rigorous data collection. The average cost savings can be compared with confidence between collection methods for the hospital setting at the individual patient level.

These results were then extrapolated using representative data to scale up results and estimate system level costs and potential cost savings, described in the results in context section of this chapter. These estimations are highly speculative but used the best available local and national data sources. They are able to provide at least some approximation and are an illustration of potential savings.

Estimated cost savings were based only on a change in practice to using voiding stimulation in favour of other non-invasive methods, rather than a change in practice to use of invasive collection methods, as described below.

6.10.5 Influence of economic evidence on practice change

6.10.5.1 Non-invasive methods

In the results in context section of this chapter, cost-savings were estimated from use of the Quick-Wee voiding stimulation method in preference to standard clean catch practice. The Quick-Wee RCT demonstrated that Quick-Wee had greater satisfaction ratings from both parents and clinicians than clean catch, [251] indicating it is acceptable for use. Quick-Wee also provides the double dividend of being both more effective and more cost-effective than standard clean catch. [251 272] Therefore it was assumed many clinicians and parents would be willing to adopt this practice change.

It was less straightforward to estimate cost savings from using Quick-Wee in preference to bag urine collection. This economic evaluation was conducted in a tertiary paediatric hospital ED setting. Bag urine collection is rarely used in this ED, and use of urine bags for culture is specifically discouraged in Australian hospital and primary care guidelines. [16 269 273 274] However, several studies in other settings have shown urine bags are used by clinicians even against local guideline recommendations. [133 142 197 275] Therefore it is less clear what proportion of clinicians might actually switch to using the Quick-Wee or clean catch methods in preference to urine bags, despite evidence for their lower costs and superior cost-effectiveness in the hospital setting.

6.10.5.2 Invasive methods

Invasive collection methods were found to have lower costs and greater cost-effectiveness than non-invasive collection methods in this economic evaluation.

However invasive collection procedures also cause substantial pain and distress for the child, [4 129 201] and these methods are not favoured by many parents and clinicians. [201] Current Australian and UK guidelines recommend clean catch collection as first line. [16 186]

As a result, it is unclear if clinicians would switch to using invasive collection methods in preference to non-invasive methods purely on the basis of costs. It is likely that many additional practical and clinical considerations would inform the decision to use an invasive collection method, and also inform choosing between catheterisation and SPA.

6.10.6 Other potential modelling

Two other plausible clinical scenarios we considered for this modelling.

The first scenario is after unsuccessful 5 minute voiding stimulation attempts, continuing waiting for clean catch collection before proceeding to catheterisation. The preceding baseline study showed that the median time for clean catch attempts in the ED was 30 minutes, 64% of first attempts resulted in urine sample collection success, and most successful collections occurred within 45 minutes. [244] A reasonable clinical plan therefore might be to attempt 5 minutes of voiding stimulation, followed by 30-40 minutes waiting for a clean catch, and proceed to catheterisation if unsuccessful at that point. Modelling for this scenario in the economic evaluation was considered.

It is however unclear how initial voiding stimulation might influence subsequent clean catch attempts. If 31% of children void within 5 minutes with voiding stimulation, compared to 12% with standard clean catch, would the additional 19% of voids happen anyway over a longer clean catch time

period? Alternately, would they not have occurred without the extra voiding stimulation? This consideration would have a significant impact on the modelling. Assuming voiding stimulation does not increase the overall likelihood of voiding and only hastens voiding for some children, voiding stimulation followed by clean catch would have a 64% success rate. Alternately assuming voiding stimulation results in additional voiding and does not reduce subsequent clean catch success, voiding stimulation followed by clean catch would have an 83% success rate. In the absence of reliable data to inform the probability of clean catch success after a voiding stimulation intervention, this scenario was not ultimately included in the modelling.

The second scenario is a 2-step model described in the literature of initial urine bag screening, followed by catheterisation for children with positive dipstick results. [210] However as previously discussed, bag urine collection is not commonly used in our setting, and this scenario is partially accounted for in the published model where children with a contaminated bag specimen may need recall for repeat collection with catheterisation (Figure 25).

6.10.7 Implications for practice and further research

Catheterisation was shown to be the lowest cost and most cost-effective collection method overall. Where invasive collection is appropriate, this study provides economic evidence to support the use of catheterisation. However as previously discussed, invasive collection is not preferred or practical in many settings.

SPA was shown to be only slightly more expensive than catheterisation. However SPA has the lowest contamination of all collection methods, [3] so may be preferred for specific clinical indications such as the septic infant. Further, the success of SPA can be increased with the use of bedside ultrasound to evaluate bladder volume, [161] where this equipment is available. Therefore although catheterisation has a small cost advantage over SPA, clinical considerations must also be considered.

Voiding stimulation was shown to be the lowest cost and most cost-effective non-invasive collection method. As a simple intervention with high parental and clinician acceptance, this study provides economic evidence to support adoption of voiding stimulation into clinical practice and guidelines where non-invasive collection is appropriate.

Clean catch collection is recommended in many current clinical practice guidelines as the first line urine sample collection method, and is non-invasive, but was shown in this modelling to be more expensive and less cost-effective than voiding stimulation. Consequently, voiding stimulation could be a recommended initial step where non-invasive collection is appropriate.

Urine collection bags were shown to be the most expensive and least cost-effective collection method. Urine bags also have the highest contamination of all collection methods, [3] and are the most time-consuming. [131] This study therefore provides additional economic evidence to dissuade clinicians from the use of urine bags, and to consider dis-endorsing their use in guideline recommendations.

Further data also demonstrates the substantial aggregate cost savings possible from the use of voiding stimulation for non-invasive sample collection in favour of the currently recommended clean catch method. At an individual hospital level at the RCH, this would save over $35000 in the ED and $60000 hospital wide annually. At a national hospital level in Australia, this would save over $600000 in EDs and over $850000 hospital wide. Adopting voiding stimulation in favour of an estimated 25% urine bag collection rate would save an additional $1.75 million.

As this economic evaluation adopted a hospital setting and costs perspective, the implications for practice are not directly generalisable to the primary care setting. Further research to define costs in the primary care setting should be considered in the future.

6.11 CHAPTER SUMMARY

The main aim of this chapter was to determine the costs and cost-effectiveness of commonly used urine sample collection methods for young pre-continent children in the hospital setting.

This is the first study to report these costs and cost-effectiveness data for all commonly used urine sample collection methods.

Invasive methods performed favourably from a costs perspective. However it is known that clinical and patient factors strongly influence the choice of collection method.

Voiding stimulation was the preferred non-invasive collection method from a costs perspective, further supporting clinical evidence from the preceding Quick-Wee RCT to adopt this method into practice.

Findings of this economic evaluation can be used to inform cost-effective clinical practice and future guideline recommendations for the hospital setting. However findings are not directly generalisable to the primary care setting.

Following on from this economic evaluation, Chapter 7 explores the barriers and enablers to using these methods in the primary care setting, to further inform guideline recommendations and future research.

Chapter 7 WHAT'S THE CATCH: QUALITATIVE ANALYSIS

"There are 3 possible explanations why one-half of UTIs are not diagnosed at the earliest opportunity in UK primary care.

First, relevant evidence in primary care regarding which children should be suspected of having a UTI is scarce. Guidelines, which emphasize the importance of fever, are largely informed by studies conducted in emergency departments.

Second, the symptoms and signs of UTI are often nonspecific, especially in very young children.

Finally, obtaining an uncontaminated sample can be challenging, time-consuming, and, for invasive catheter and suprapubic aspiration sampling methods, painful and frightening".

Hay et al (2016) [43]

7.1 OVERVIEW

This chapter describes the third part of the thesis research, the What's The Catch qualitative study.

Sections 7.2-7.7 includes the rationale for the research, background and literature review specific to the qualitative study, aims, hypothesis, and methods.

Section 7.8 includes results and the article in press outcomes paper.

Section 7.9 discusses the strengths and limitations of the study, and implications for practice and further research.

PAPER 6: QUALITATIVE STUDY

The article in press qualitative study (Paper 6) forms part of this chapter:

6. **Kaufman J**, Temple-Smith M, Sanci L. What's the catch? Urine sample collection from young pre-continent children: a qualitative study in primary care. *British Journal of General Practice Open*. In press (accepted for publication 28th February 2020). doi: 10.3399/bjgpopen20X101060

7.2 RATIONALE

As described previously in Chapter 2, UTIs are common in young children, and if unrecognised further complications can occur. A urine sample must be obtained to diagnose or exclude UTI. Collecting a urine sample from young pre-continent children however is challenging, and current collection methods all have limitations. Current international guidelines have conflicting recommendations for the optimal collection method. Difficulties in obtaining a satisfactory sample leads to misdiagnosis and missed diagnosis of UTI. Many children are prescribed antibiotics for UTI without any urine sample being collected at all.

Chapters 4 and 5 of this thesis introduced the novel Quick-Wee voiding stimulation method, and comprehensive evidence that Quick-Wee improves the speed and success of clean catch collection in the hospital setting. Chapter 6 of this thesis, the Liquid Gold health economic evaluation, demonstrated from a hospital costs perspective that catheterisation is the favoured collection method overall, and voiding stimulation using Quick-Wee is the favoured non-invasive collection method.

However clinical practice in primary care has unique time and resource constraints compared to the hospital setting. Guideline recommendations for collection methods are mostly based on studies conducted in the hospital setting, which may not adequately reflect the pragmatic considerations of the

primary care context. Targeted research is required to understand the optimal collection methods for the primary care setting.

7.3 BACKGROUND

7.3.1 Prevalence of UTI in young children in primary care

As described in Chapter 2, UTI in young children is common in general and commonly seen in primary care, with a reported prevalence of 2-6% in UK primary care. [43] [211] One Australian study found that approximately 1% of GP consultations for children aged 0-16 years recorded a new UTI as the problem or diagnosis. [276]

Children presenting to primary care with signs and symptoms suggestive of UTI must have a urine sample collected to confirm the diagnosis. Many more children who present with unexplained fever will also require urine sample collection to diagnose or exclude UTI, as recommended by NICE and other guidelines. [186]

Collecting urine samples from young pre-continent children is therefore a ubiquitous part of practice for many primary care clinicians.

7.3.2 Primary care and general practice in Australia

Primary medical care in Australia is predominantly provided by general practitioners (GPs), who are specialist primary care doctors trained under the auspices of the Royal Australian College of General Practitioners. In other countries GPs are known as “family physicians” or “family medicine doctors”.

The Australian primary health care system is a hybrid mix of the UK publicly funded and US privately funded systems. Although many general practices in Australia are privately owned businesses, the majority of consultations and services are subsidised by the Australian government funded national Medicare system, [277] similar to the UK National Health Service (NHS). Though

general practice is the cornerstone of primary care in Australia, primary care is also delivered in community health centres and aboriginal health services.

7.3.3 Diagnosing UTI in young children in primary care

It is estimated up to 50% of UTIs in young children are missed on initial presentation to primary care. [41 43] Suggested reasons include the inability of pre-verbal children to articulate symptoms, the difficulties of parents and clinicians observing clinical signs in nappy-wearing children, and the difficulties obtaining the required urine sample which can be frustrating, time-consuming and costly. [41]

These difficulties likely exist across all settings, but their manifestations, significance and suitable strategies to overcome them may differ between hospital and primary care settings. The major research question of this doctoral thesis aims to address the third of these reasons: finding a strategy to overcome the challenges of urine sample collection. This chapter now focuses on how clinicians collect urine samples from young children in primary care, to highlight similarities and differences to practice in hospital settings, and to understand the unique barriers and enablers that exist in the primary care setting.

7.4 LITERATURE REVIEW: ATTITUDES & PRACTICE PATTERNS

A targeted literature review was undertaken to inform the qualitative study design. Studies were included in the final evidence summary if they examined:

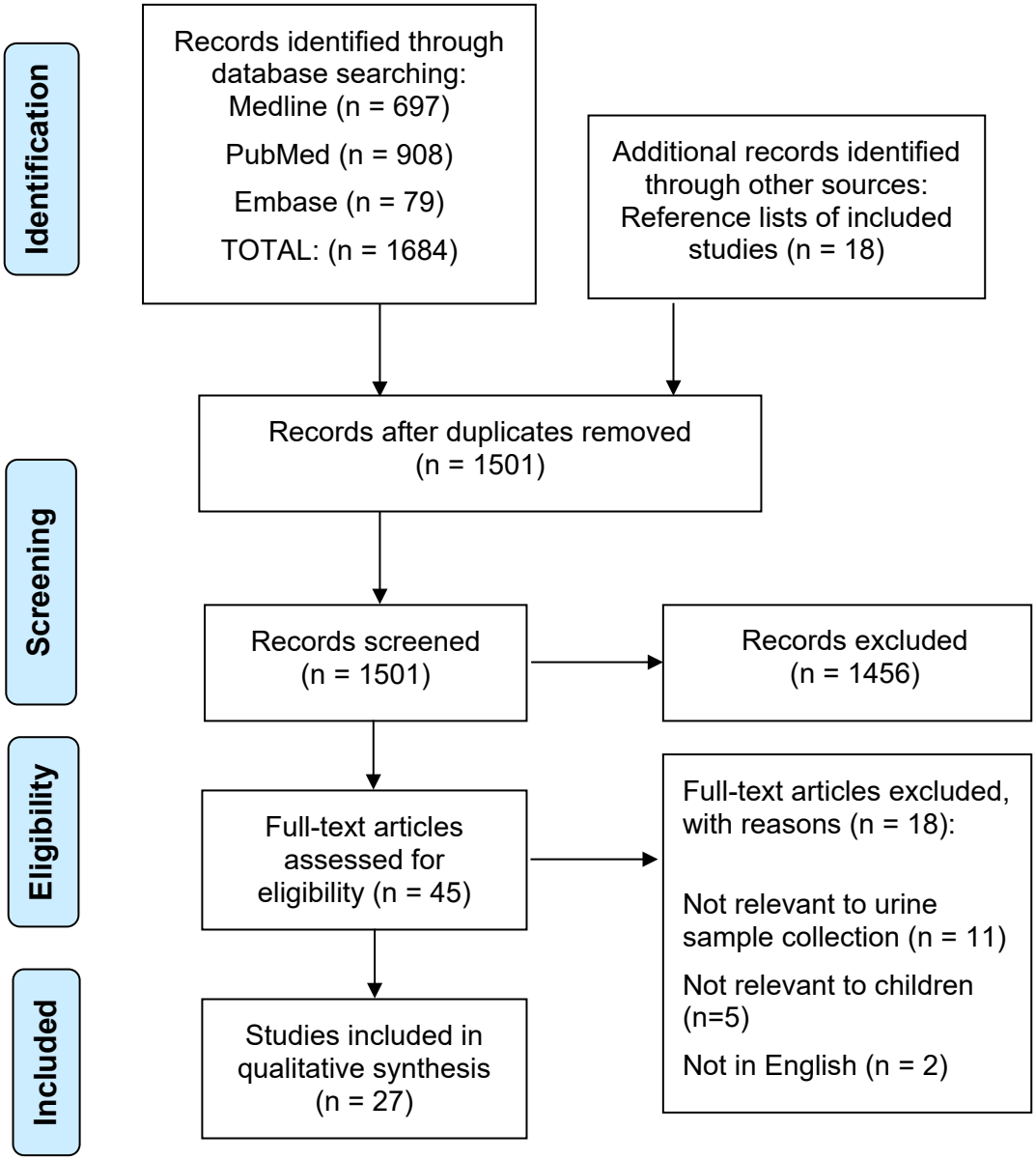
1. Practice patterns and attitudes to urine sample collection methods
2. Qualitative research into urine sample collection methods

Ms Poh Chua, RCH Senior Librarian, provided assistance with designing and refining the literature review strategy.

Databases searched included Ovid Medline, PubMed and Embase. Further targeted searching from reference lists and relevant guidelines was performed. While search terms varied slightly between databases, they effectively focused on the terms “child”, “urinary tract infection”, “urine specimen collection”, “attitudes of health professionals”, “knowledge”, “attitude”, “survey”, “audit” and “qualitative research”. Full details of the search strategy and search terms is included in Appendix 11.6.3.

Figure 26: Qualitative study: literature search summary

Attitudes, practice patterns and qualitative studies. PRISMA flowchart [231]



The literature review included studies from all clinical backgrounds and settings, to identify existing knowledge and where knowledge may be lacking, and to enable results to be compared and contrasted between hospital and primary care settings.

25 relevant studies and 2 editorials were identified (Figure 26), published between 1984-2017:

- 8 from GP settings (UK, Ireland, Netherlands) [126 146 193 278-282]
- 12 from paediatric settings (US, UK, Europe) [124 125 134 195-198 283-286]
- 4 from ED settings (Australia, Netherlands, Canada) [142 165 275 287]
- 3 specific to parents (US, UK) [136 200 201]

Only two studies utilised a qualitative methodology, one was a questionnaire for GPs with quantitative and qualitative items, [282] and one was a semi-structured questionnaire for parents which included some qualitative questions. [200] Other studies utilised quantitative methodologies including surveys, questionnaires, audits, and observational cohorts.

The individual studies are described with further detail in Table 15 of Appendix 11.6.3, and the overall relevant findings from this literature review are summarised in this section.

7.4.1 Critical summary of findings

Clinicians making decisions about urine sample collection methods have different professional (medicine, nursing) and speciality backgrounds (general practice, paediatrics, emergency medicine) and work in different settings (primary/community care, ED, hospitals).

There is significant variation in clinician preferences and practice for how to collect a urine sample from young children. [125 126 134 142 196 198 284] There is variation both within and between specialties, and between geographic areas. [134] There is a strong preference in some settings for the use of urine bags, [126]

[134] despite their high contamination rate. Previous research in Australian settings is limited to one study, [142] which found variation in preferences between Australian ED physicians.

Clinicians across the specialities did not always follow local guideline recommendations for managing UTI in young children, or the recommended method of urine sample collection. [125 142 195-197 275 286] It has been noted that guidelines are predominantly informed by evidence from large studies based in the ED setting, and it has been suggested that some guidelines may be too complex. [281]

Urine samples are not always collected for children with unexplained fever or suspected UTI, against guideline recommendations. [124 193 198 275 282] Many UTI diagnoses in young children occur without any urine sample for confirmation. [146 275 278 280 286] Practical difficulties in obtaining a sample was a commonly cited reason for why a sample may not be collected, [146 198 280 282 285] but the actual barriers and enablers to sample collection are not well defined.

There is conflicting data from parents about their preferred collection methods, [200] but overall many parents report the process is difficult, time-consuming, messy, and can be distressing for the child. [136 200 201]

7.4.2 Findings specific to primary care

Two questionnaire based studies reported that urine bags were the preferred collection method in UK and Irish general practices, [126 282] but several studies noted that UTIs were often diagnosed without culture confirmation from a urine sample in primary care settings. [146 193 278 282 288]

Several studies mentioned barriers to urine sample collection from young children, but with limited detail [193 279-281] Two questionnaire based studies (Van Der Voort 1997, Vernon 1997) did explore some of these barriers in the UK general practice setting, but these studies are now dated. [146 282]

7.4.3 Implications of the literature review

Most children with unexplained fever or UTI who require urine sample collection present to primary care, yet most research regarding barriers to collection has been conducted in hospital and specialist settings.

No previous studies have adequately explored the barriers to urine sample collection from young pre-continent children in the primary care setting, and few studies have identified the enabling factors which may allow urine sample collection to occur.

This study aims to address this identified gap in the literature, focusing on the Australian primary care setting.

7.5 AIMS

7.5.1.1 Primary Aim

The primary aim of this qualitative study was to:

I. Explore and characterise the barriers and enablers to collecting urine samples from young pre-continent children in the Australian primary care setting.

7.5.1.2 Secondary Aims

Secondary aims of this qualitative study were to:

I. Synthesise these findings to highlight the challenges of UTI diagnosis for young children in the primary care setting.
II. Inform future guideline recommendations for urine collection strategies that are suited to the primary care setting.
III. Inform, guide and direct future research in this field, targeted at developing urine collection strategies suited specifically to young children in the primary care context and setting.

7.6 HYPOTHESES

The doctoral candidate hypothesised that:

I. The primary care setting would have different barriers and enablers to sample collection compared to the hospital setting.
II. Primary care clinicians would have preferences for collection methods which are influenced by the nature of the primary care setting.

7.7 METHODS

This was a qualitative research study, with semi-structured interviews of GPs and practice nurses involved in collecting urine samples from young pre-continent children in primary care.

The methods for the qualitative study are included in Paper 6, with further relevant detail outlined in this section.

The plain language statement, consent form, and full interview schedule are included in Appendix 11.5.

7.7.1.1 Study management, roles and responsibilities

The doctoral candidate was the lead researcher and clinician responsible for initiating, co-ordinating and implementing the study.

Professor Lena Sanci and Professor Meredith Temple-Smith advised on developing the research question, study design and methodology, supervised development of the interview schedule, and supervised the analyses.

The doctoral candidate wrote the first and final versions of the study protocol, ethics application and manuscript, which were reviewed by all co-authors.

7.7.2 Reporting guidelines: SRQR and COREQ

The doctoral candidate followed the relevant international reporting guideline statements when designing the study methods and reporting study results for this qualitative study.

The Standards for Reporting Qualitative Research (SRQR) checklist contains a synthesis of recommendations for reporting qualitative research. [289] The SRQR checklist was submitted with the study manuscript at the time of publication.

The COnsolidated criteria for REporting Qualitative research (COREQ) is an alternative reporting guideline also recommended by the Equator network and some journals. [290] Additional reporting items from the 3 domains of the COREQ checklist, which were not completely addressed in the published paper or SRQR checklist, are outlined in this section.

7.7.3 Domain 1: Research team and reflexivity

7.7.3.1 Personal characteristics of the interviewer

All interviews were conducted by the doctoral candidate, who is a male paediatrician, and had undergone introductory training in qualitative research methods.

7.7.3.2 Relationship with participants

Two participants had previously worked as trainees in the same hospital department as the interviewer: seven and eight years prior respectively. Two participants had academic appointments in the same university department as the interviewer, but neither worked directly with them.

As part of the plain language statement, informed consent process, and interview pre-amble (see Appendix 11.5), all participants were informed that the interviewer was a PhD student and paediatrician, and that the research would form part of a PhD thesis chapter.

Four participants mentioned being specifically aware that the interviewer had developed the Quick-Wee voiding stimulation method, through reading journal articles or attending departmental education sessions.

7.7.4 Domain 2: Study design

7.7.4.1 Theoretical framework

Qualitative research provides a rich, in depth description of an issue and allows examination with the context of everyday life. It is especially useful to highlight the breadth of practice and opinion, where participants are not constrained by responding to a limited set of specific questions. This can provide a more detailed exploration of the topic, and allow nuances and subtleties to be teased out. Qualitative methodologies and theories are not homogenous, with similarities and differences across approaches. [291]

The study adopted a general inductive-deductive approach, to maintain flexibility with the analysis. Inductive research aims to collect data and then look for patterns in the data. [292] Theories that explain those patterns can then be proposed. In other words and as visually represented in Figure 27, inductive research moves from the specific (data) through observation (analysis) to the general (theories). This study adopted a predominantly inductive approach. Deductive research starts with a general theory and moves to a more specific focus. [292] The deductive element of this research was the hypothesis that barriers and enablers to urine sample collection in primary care exist in the first place. It is recognised in the literature that inductive and deductive approaches can be complementary, and both approaches may be utilised within a body of work. [292]

Figure 27: Inductive research approach



Figure adapted from Principles of Sociological Inquiry: Qualitative and Quantitative Methods [292]

7.7.4.2 Participant selection

Purposive sampling was used as described in the article in press paper.

GPs and practice nurses (PNs) were initially approached via the Victorian primary care practice-based Research and Education Network (VicReN). VicReN is the University of Melbourne Department of General Practice's practice based research network. Recruitment methods included announcements in the VicReN newsletter and in emails sent by the VicReN co-ordinator. A brief promotional video with information about the project was also produced for the VicReN YouTube channel, as well as flyers for interested practices (click hyperlinks to view these resources).

Additional GPs and GP clinics known to the research team from previous studies and professional networks, or who expressed an interest in the study, were also invited to participate by email.

Snowball sampling was used to identify further participants.

25 out of 35 GPs and PNs who were contacted agreed to participate. 10 GPs and GP clinics who were contacted by email did not respond, but none directly declined to participate in the study.

7.7.4.3 Setting

Face to face interviews were held at the participating clinic or the University of Melbourne Department of General Practice during opening hours. Telephone interviews were conducted at a mutually convenient time.

Only the participant and the interviewer were present for each interview.

The characteristics of the sample including participant demographics and practice type are included in Table 1 of Paper 6.

Details of the study risk management strategy, data storage, confidentiality and privacy plan were outlined in the study protocol which received ethics approval from the Department of General Practice Human Ethics Advisory Group, University of Melbourne.

7.7.4.4 Data collection

The interview guide is provided in Box 1 of Paper 6. The full interview schedule including the interview pre-amble and open question prompts are included in Appendix 11.5.2.

Initially, a series of demographic questions were asked relating to the GPs' age, gender, years working in general practice, country where medical degree was obtained, level of training, further qualifications, special clinical interests, clinic postcode (rural/metro) and practice profile.

Then a series of scenario based questions relating to a hypothetical clinical case and the following topics were explored:

- Preferred method of collecting urine samples from young children
- Why that method was preferred
- Factors that facilitate sample collection
- Factors that obstruct sample collection
- Other collection methods considered and reasons for preferences

A range of prompts were used to elicit details in each category. The interviews followed the interview guide but also included additional open questions to allow for in-depth information and personal statements.

The interview schedule was piloted by the doctoral candidate on two GPs (one fellow and one registrar), and some minor adjustments were made in consultation with the study co-authors.

Participants were made aware that the interviews would be audio recorded (with their permission). Interviews were recorded using an Olympus digital recording device.

25 interviews were conducted as described in the published paper, until data saturation was reached and no new themes were emerging.

Reflexive field notes were recorded immediately after each interview, considering (if applicable) any factors which may have influenced the data collection and interview process or which could influence the data analysis.

Interviews were transcribed verbatim from the audio recordings. 5 were transcribed by the doctoral candidate. 20 were transcribed by a commercial transcription company and these transcripts were then checked by the doctoral candidate. Transcripts were not returned to participants for comments or corrections.

7.7.5 Domain 3: Analysis and findings

7.7.5.1 Data analysis

Following transcription of the interviews, the data collected was analysed for content. The data was analysed as described in Paper 6, with further detail about the analysis as follows.

Data was analysed systematically using a general inductive-deductive approach as previously described. The processes of thematic analysis are outlined in Table 9.

Table 9: Phases of thematic analysis

Phase	Brief description of process
1. Familiarisation with the data	Transcribe and read data Note initial ideas
2. Generate initial codes	Code data systematically Collate data relevant to each code
3. Identify themes	Collate codes into potential themes Gather data relevant to each theme
4. Review themes	Check themes by data extracts & data set Generate thematic map of analysis
5. Define and name themes	Ongoing analysis to refine themes Refine overall story the analysis tells
6. Report analysis	Select compelling examples Relate analysis back to research question

Table adapted from Braun & Clarke, Qualitative Research in Psychology 2006 [291]

Each transcript was analysed individually and assigned codes using NVivo 12 software. [293] NVivo is a qualitative data analysis program produced by QSR International, designed for text-based information.

The codes were then used to build an indexing system for the data, reflecting the core concepts deemed to be the most important. Recurring patterns of interest in the data were identified as themes. Emerging themes were used for

ongoing reflection and for comparison with new data. Coding was discussed within the research team to achieve consensus on the common themes derived from the data.

Data was analysed iteratively to identify major themes, and subthemes within major themes. The final analysis contained 5 main themes and 19 sub themes which emerged from the data.

7.7.5.2 Reporting

Participant quotations were presented to illustrate each theme and subtheme. Quotations were identified by the participant number and type of practitioner (e.g 4 urban GP or 24 rural PN). Additional exemplar quotations for each theme and subtheme were included in Supplementary Table 1 of Paper 6. Major themes and minor subthemes were clearly identified, as well as additional discussion of diverse cases.

7.8 RESULTS

7.8.1 Article in press results paper (Paper 6)

The results of the trial were accepted for publication in the journal *British Journal of General Practice Open*, and the in press manuscript is included below.

BJGP Open

What's the catch? Urine sample collection from young pre-continent children: a qualitative study in primary care.

Journal:	*BJGP Open*
Manuscript ID	BJGPO-2019-0100.R1
Manuscript Type:	Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Kaufman, Jonathan; The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, General Practice; Sunshine Hospital, General Paediatrics; Murdoch Childrens Research Institute, Health Services Research Group Sanci, Lena; The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, General Practice Temple-Smith, Meredith; The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, General Practice
Keywords:	urine specimen collection, infant, general practice

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Manuscripts

What's the catch? Urine sample collection from young pre-continent children: a qualitative study in primary care.

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Keywords: urine specimen collection, infant, urinary tract infection, paediatrics, general practice

How this fits in: Collecting a urine sample to diagnose or exclude UTI in a young child can be challenging, and existing collection methods all have limitations. This qualitative study found that non-invasive collection methods were strongly preferred in primary care, although clinicians thought that clean catch could be time-consuming and urine bag samples were often contaminated. Barriers to collection included the time and resource constraints of the primary care setting, and enablers included parental motivation to collect samples and voiding stimulation methods.

Word count: Abstract 249 words, Main Text 4071

ABSTRACT

Background:
Urinary tract infections (UTI) are common in young pre-continent children, but collecting urine samples is challenging. Collection methods all have limitations and international guidelines have conflicting recommendations. Choice of method must balance time, resources, invasiveness, reliability, and contamination. Evidence from primary care clinicians is limited regarding barriers and enablers to sample collection, and what factors inform the choice and use of different sample collection methods.

Aim: To understand the barriers and enablers to collecting urine samples from young pre-continent children in primary care.

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Design, Setting, Methods: An exploratory qualitative study. Semi-structured interviews explored the topic with 21 Australian General Practitioners and 4 Practice Nurses until data saturation was reached. Interviews were audio-recorded, transcribed verbatim, coded, and underwent content and thematic analysis.

Results: 5 main themes emerged including the clinician's knowledge and expertise, patient characteristics, parent/carer's understanding and motivation, the collection process itself, and likely outcome of the chosen method. Non-invasive methods were strongly favoured, though clean catch was considered time-consuming and urine bags were known to be often contaminated. Invasive methods (catheterization, suprapubic needle aspiration) were rarely performed outside of remote settings. Key barriers included time and space constraints in clinics, and key enablers included parental motivation, education handouts and voiding stimulation methods.

Conclusions: This study has identified key barriers and enablers to inform education, policy and future research for urine sample collection from pre-continent children in primary care. Guidelines recommendations must consider the primary care context to ensure recommendations are relevant and suited to real world practice.

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INTRODUCTION

Urinary tract infections (UTIs) are common in early childhood, affecting 2-6% of febrile young children in UK primary care. [1 2] If untreated UTI can cause significant complications including sepsis, meningitis and renal scarring. However clinical signs are often non-specific, and overlap with many viral infections as well as other bacterial infections such as otitis media. Therefore UTI may not be considered or evaluated on initial presentation, and so the diagnosis is often delayed or missed in primary care. [3 4] UK guidelines therefore recommend that any young child with signs and symptoms that could suggest UTI, or unexplained fever, should have a urine sample tested. [5]

Collecting a urine sample from a young pre-continent child is challenging though, and limitations exist with all current urine collection methods. These include non-invasive (urine bags, pads, clean catch) and invasive (catheter, suprapubic needle aspirate) methods. Once the decision to collect a sample has been made, choosing the method of urine sampling involves balancing the pros and cons related to time, resources, experience, invasiveness, reliability, and contamination rates. [6]

Australian and UK guidelines recommend clean catch as the first line collection method, [5 7] but as few as 20% of general practitioners (GPs) use this method. [8] Several guidelines specifically discourage the use of urine bags for culture due to high contamination and false

positive rates, [6 7 9] but they are often favoured in primary care. [8 10] Over 30% of children under 2 years of age are diagnosed and treated for UTI without subsequent culture confirmation in some settings, [11-16] despite recommendations this should occur when UTI is suspected. [5-7 9]

What is not well characterised is the reason for these choices, or what challenges are faced in collecting urine samples from young children in primary care. Limited evidence regarding barriers to collection comes mostly from studies in the hospital and emergency department (ED) setting, [10 17] or surveys of parents. [18 19] While this data suggests that practical difficulties are common, primary care has unique time and resource constraints compared to the hospital setting. Two questionnaire based studies in primary care from 1997 partly identified some of these barriers such as practical problems with collection, [14 15] but did not explore different collection methods in detail.

To our knowledge there are no previous studies using interview based qualitative research regarding clinician's choice and use of urine sample collection methods for young children, and the practicalities of collection, in the primary care setting. There is a need for further primary care research to ensure guideline recommendations are relevant to real-world practice. Qualitative research is particularly suited for the context where little is known about a topic, as it allows issues to be examined in depth. [20] The aim of this study therefore was to explore the barriers and enablers to collecting urine samples from young pre-continent children in the primary care setting.

METHODS

Setting & Recruitment

In the Australian primary health care system most practices are privately owned by groups of GPs or corporations. The national government health system Medicare funds or subsidises most consultations and services, but around 30% of Australians have out-of-pocket costs from seeing a GP. [21] Purposive sampling was used to recruit a representative range of participants to broadly reflect the spectrum of the Australian primary care workforce by age, sex, rurality and type of clinic.

Australian GPs and practice nurses (PNs) were recruited via the Victorian primary care practice-based Research and Education Network (VicREN), [22] and professional networks. VicRen is a research and education network enabling collaboration between over 600 GP practices and the University of Melbourne Department of General Practice. Thirty-five practices and individual GPs were contacted by email or phone and invited to participate.

Interviews

Participants gave written consent to participate. Semi-structured interviews were conducted in person or by telephone, between November 2018 and April 2019, until data saturation was reached. An interview guide included demographic questions, followed by a scenario based question related to a hypothetical clinical case, with further open questions exploring the topics outlined in Box 1. The scenario situated the conversation in the context of sample collection, once the decision to collect a sample had been made. The lead researcher conducting the interviews was a paediatrician and PhD candidate with research expertise regarding paediatric UTI, urine sample collection and voiding stimulation methods. [23-25]

BOX 1: INTERVIEW GUIDE

SCENARIO

You see a febrile, 6 month old child with fever and vomiting. On examination there is no focus for their fever, and they are not otherwise unwell. The child is still feeding normally. The parents report the urine has a different smell than usual. Would you collect a urine sample as part of their care?

TOPICS

- Preferred method of collecting urine samples from young children
- Why that method was preferred
- Factors that facilitate sample collection (enablers)
- Factors that obstruct sample collection (barriers)
- Other collection methods considered and reasons for preferences

No financial incentives were offered to individual participants, but participating clinics were offered a 30 minute child health education session provided by the lead researcher.

Interviews lasted 14-36 minutes (mean 24) and were audio recorded, transcribed verbatim, de-identified and checked. Reflexive field notes were made following each interview.

Analysis

NVivo 12 software was used to code transcripts and organise data. Data was analysed using an inductive-deductive approach. A coding schema was developed based on the first three interviews, and refined iteratively. A subset of three interviews was analysed by all members of the research team independently, to discuss and reach consensus for the coding framework. Codes were then grouped according to themes and sub-themes. Reporting followed the Standards for Reporting Qualitative Research (SRQR) Guidelines. [26]

RESULTS

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Twenty-five interviews were undertaken with 21 doctors and 4 nurses, with a range of personal and professional characteristics and from a variety of clinics reflecting the breadth of primary care in Australia. (Table 1)

TABLE 1: PARTICIPANT AND PRACTICE CHARACTERISTICS (N=25)

Participant Characteristics	
Age (range)	Mean 45 years (31-67)
Gender	
Male	9 (36%)
Female	16 (64%)
Country of primary medical/nursing degree	
Australia	22 (88%)
UK	1 (4%)
Ireland	1 (4%)
New Zealand	1 (4%)
Years working in general practice* (range)	Mean 14 years (1-39)
Full or part time	
Full time	13 (52%)
Part time	12 (48%)
Training level	
GP fellow	16 (64%)
GP registrar	5 (20%)
Practice nurse	4 (16%)
Proportion of usual patient load with children (range)	Mean 24% (2-100%)
Special interest in paediatrics	Yes 11 (44%)
	No 14 (56%)
Additional postgraduate qualification in paediatrics or child health	
Diploma	5 (20%)
None	20 (80%)
Practice Characteristics	
Location	
Inner	8 (32%)
Outer Urban	3 (12%)
Regional	8 (32%)
Rural	4 (16%)
Remote	2 (8%)
Number of full time equivalent GP's at clinic (range)	Mean 6 (2-10)
Number of full time equivalent PN's at clinic (range)	Mean 2 (0-4)
Type of clinic	
Private	14 (56%)
Mixed Community/Private	6 (24%)
Community Aboriginal Health	3 (12%)
Community Refugee Health	1 (4%)
Corporate	1 (4%)

* years working in general practice does not include hospital training

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Preferred collection method

Clean catch was the preferred collection method for a febrile 6 month old child (Box 1) for just over half of the clinicians (14/25), mostly preferred for its lower contamination than other non-invasive methods.

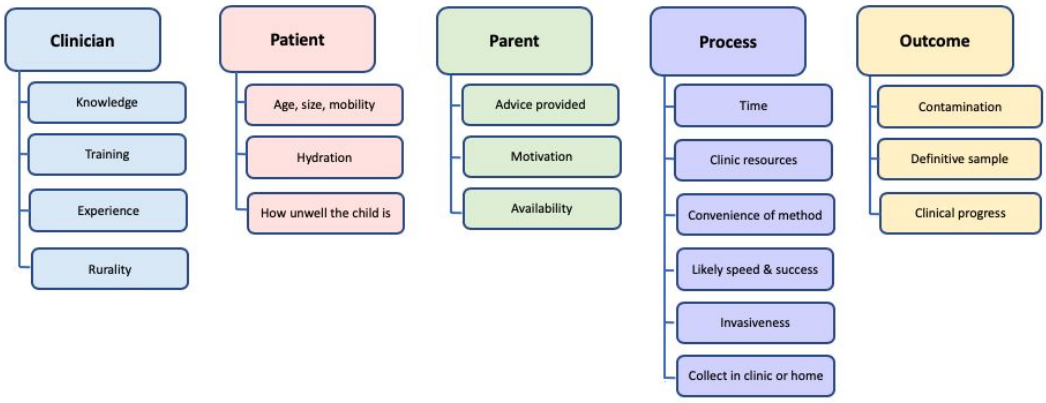
Urine bags were preferred by almost all the remaining clinicians including all 4 PNs. Urine bags were mostly preferred for their convenience because clean catch was perceived to be time-consuming and difficult. One clinician reported preferring cotton wool balls due to convenience.

No clinicians used invasive collection methods as first line. Invasive methods were regarded as impractical or unnecessary in primary care, and more suited to unwell children in the hospital setting. Some rural and remote clinicians reported using clean catch for most children, and catheter or SPA if the child was more unwell.

Themes

Five main themes and 19 sub themes emerged from the analysis for the barriers and enablers to collecting urine samples from young children. These comprised clinician's knowledge and expertise, patient characteristics, parent/carer's understanding and motivation, the collection process itself, and likely outcome of the chosen method (Figure 1). A list of further example quotes from each theme and sub-theme is included in Supplementary Table 1.

FIGURE 1: BARRIERS AND ENABLERS TO URINE SAMPLE COLLECTION FROM YOUNG CHILDREN: THEMES AND SUB-THEMES



CLINICIAN FACTORS

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Knowledge. Theoretical knowledge about collection methods was varied amongst clinicians, but knowledge of likely contamination rates, particularly for urine bags, was commonly reported.

"*And you can use urine bags, but, my understanding anyway, is that they're much more prone to contamination. So we try to steer away from those if possible." (3, urban GP)*

A minority of clinicians held differing views regarding likely contamination for bag samples.

"I find that I get very clean samples. And so yeah, I generally don't get any squames or very rarely in my samples, so I'm very happy with the accuracy of it." (4, urban GP)

Training. For many clinicians their knowledge and preference for collection methods was strongly influenced by their previous training, both in hospital and in GP settings.

"Because of my training at the children's hospital when I was a young GP" (1, urban GP)

"*I think my GP supervisor when I was training, he did it. And that's where I learnt it." (14, urban GP)*

Experience. Several clinicians learnt how to perform catheterisation or SPA during hospital paediatric training terms. However infrequent ongoing practice in the GP setting resulted in them no longer feeling confident to perform these procedures.

"I haven't done a suprapubic aspiration for a while now, so I could certainly try, I know the theory behind it, but I have a feeling that I may not be successful. So I think lack of practice, probably would slightly caution me." (17, urban GP)

Rurality. Geography and practice location frequently determined how likely GPs were to perform invasive collection methods. In urban and regional areas, many clinics were located close to a hospital.

" being close to a paediatric emergency department I think I would be sending them in, rather than completing that procedure" (2, urban GP registrar)

In rural and remote areas, GPs often performed invasive collection procedures, as the clinicians working at the local hospital or in isolated locations.

"I think in general our rural colleagues do a lot more procedures than we do. Often they are on call for the base hospital." (17, urban GP)

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"*I was in remote Queensland… So I did everything out there." (12, urban GP)*

PATIENT FACTORS

Age, size, mobility. Patient factors were a commonly mentioned barrier in relation to clean catch collection, particularly for older and more mobile children.

"And certainly if the child is distressed and uncooperative and won't sit still, that's really tricky." (11, urban GP registrar)

Hydration. All clinicians considered hydration status to be important, with poor hydration being a barrier, and optimising hydration being an enabling strategy for collection success.

"If they're really dehydrated, you're not going to get much urine out" (8, regional GP registrar)

How unwell the child is. The clinical state of the child strongly influenced whether clinicians felt the child should be referred to hospital for invasive sample collection and further assessment.

"if… something about their clinical examination makes me concerned, I don't think sending the family home would be appropriate in that setting, and I would send them off to the hospital." (17, urban GP)

PARENT/CARER FACTORS:

Advice. The explanation and advice given to parents and carers was seen to strongly influence collection success, as in most cases parents enacted the actual collection process. Several clinicians felt it was important that parents understood why collecting a sample was important, as well as the logistics of the actual collection process.

"the better they understand that generally the more persistent they are, and successful getting the sample" (3, urban GP)

Printed handouts were identified as a valuable tool to educate and engage parents, enable collection success, and save time.

"A lot of people take information in differently, and a lot of people are overwhelmed by words, and just words on a page, I think visual instructions are always helpful." (13, regional GP registrar)

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Motivation. Many clinicians described the importance of parents being motivated to collect a sample, which was further enabled by parental health literacy. This was particularly the case for successful clean catch collection, which could be time-consuming or difficult.

"So clearly some parents are really good at following instructions, you know, "Yes, we've gotta get this done," and others, I don't know, get caught up in other things." (11, urban GP)

Availability. However, for families with multiple children, or other resource limitations, clinicians recognized that collection could be challenging.

"if they've got multiple other kids just the logistics of not being able to be two places at once" (7, regional GP registrar)

PROCESS FACTORS

Time. Time availability in primary care was identified as a major barrier to sample collection, and significant influence on the choice of collection method.

"*Probably using the bag, simply because, time is often... a bit pressed for time yeah. Its often very busy" (10, regional PN)*

Several GPs discussed that if collection was going to take a long time, then in practice this would then need to happen at home.

"…often it's a time-consuming thing trying to get a sample from an infant and it's time the doctors don't have" (24, rural PN)

Clinic Resources. The availability of a suitable space also limited capacity for clean catch collection, and for invasive procedures.

"You can't just sit them in the waiting room without their nappy on. I mean, you could but we generally choose not to because I think it would put other people off." (11, urban GP)

Separate treatment rooms or an unoccupied consulting room were an enabler, but this was available in a minority of clinics.

"GP clinics are run to make sure that rooms are occupied. So, room availability can be an issue." (13, regional GP registrar)

Some clinics had practice nurses who were able to help with sample collection.

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"In my practice its good because I have skilled nurses who can follow that up, so I can still be seeing other patients while we wait for that sample." (2, urban GP registrar)

However often the nursing staff were also busy, or not available at the time required.

"…we're not very well staffed with nurses, and the nurse is super busy doing other things." (18, urban GP)

Convenience of method. Collecting urine samples from young children was generally regarded as a challenging process.

"… as soon as you hear "fever" there's always that little part of you that says "I bloody hope I can find a source here, because if I can't find a source, it's going to be a pain in the ass trying to get that urine sample". (3, urban GP)

The perceived convenience of urine bags, for both the clinician and family, was a strong consideration for the clinicians who favoured their use.

"I actually do like that bag collecting method. I think that's something that's a little easy. You can pop that on a child and perhaps set and forget for a bit, rather than standing there with a cup, hoping and waiting." (13, urban GP registrar)

In contrast clean catch was often seen to be inconvenient, often related to the attention required from parents.

"*In my experience, parents often say, "Oh, we can't do it," or "It's too hard."" (1, urban GP)*

Likely speed and success. Whether collection occurred in the clinic or at home, the likely speed and success of the collection method was a strong consideration for many clinicians. There was a consistent sense that clean catch collection was often time-consuming, therefore would often be something parents needed to do at home.

"I think it's an excellent method, but it's obviously very time consuming" (4, urban GP)

While some clinicians felt that successful clean catch collection was very unlikely, others felt that most clean catch attempts were successful.

"a clean catch is nearly impossible ... fluky if you can do it" (6, regional GP)

"I've found most parents have come back with something." (7, regional GP registrar)

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Some GPs reported difficulties with urine bag collection as well.

"It is just difficult to get those urine bags to work, difficult to apply, difficult to get a clean sample. So I'm not sure what the percentage would be, but lots of the time the parent comes back and says it's just leaked and they haven't been able to get anything." (5, regional GP)

Clinicians were interested in ways of improving the speed and success of collection.

"Definitely. If there were sort of practical, simple things that would make it easier to collect. Yes, I would be very keen to try that." (19, remote GP)

Voiding stimulation methods, such as the Quick-Wee technique, [23] were felt to improve the speed and success of clean catch collection.

"…one way to try and get the urine sample without having to wait for too long is to get the nappy off and then get a cool cloth and then rub in a circular motion just above the pubic bone where the bladder is, and sometimes it will induce a reflex where it starts urination, and you collect a sample from there." (3, urban GP)

Clinicians perceived these methods, when they knew about them, as simple to incorporate into practice, and acceptable to parents.

"I learned that in my hospital time, where I was doing it. And I think also from the nursing staff. Can't remember, but anyways, it's been quite successful." (21, urban GP registrar)

This timeliness of collection also influenced whether the child would need to attend hospital.

"If we weren't getting a quick sample, I may consider referring them into the Emergency Department." (2, urban GP registrar)

Invasiveness. Using a catheter or needle to extract urine directly from the bladder was seen as highly invasive.

"…there's the impression that it's, well, it's not a pleasant thing to do, it's really invasive, it's a bit of a nasty thing to do." (5, regional GP)

It was also thought that parents would not consider invasive methods acceptable outside the hospital setting, unless in rural or remote locations.

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"I think the idea of a percutaneous intervention for an infant or baby is quite intimidating for a parent. They may not understand the relevance or appreciate the significance of it in a general practice setting, but in the hospital setting where there is generally a higher acuity of pathology, I think parents are more accepting of the need to undergo such a procedure." (17, urban GP)

Collection in clinic or at home. For the preferred non-invasive collection methods, clinicians varied in whether collection usually occurred in the clinic or at home.

"I do try to get them to do that while they're in the clinic, which, again, most parents are pretty happy to do" (19, remote GP)

"…well in our particular practice, um, we'll encourage them to catch the urine at home" (12, urban GP)

Collection at home also raised possible logistic challenges, and concerns that parents may not return with the requested sample.

"*If you see them for example at 12:30 on a Saturday and the clinic center closes at two, how are you gonna deal with that if they manage to collect the specimen at 5 or 6, who's actually gonna do the dipstick and how would you deal with that." (1, urban GP)*

Many clinicians reported initially trying to collect a sample in the clinic, but sending the child home for continued collection attempts if required.

"We'll just get the jar ready and if they start to pee, we'll catch the specimen or then I'll give the jar to the parent and get them to wait and watch while I type up notes or do other things. And then if everything's done and we still don't get a specimen, then I might send them home to do it." (11, urban GP)

OUCTOME FACTORS

Contamination. Contamination was a recurring theme during interviews. Most clinicians were aware that urine bags had high contamination, but this did not always deter them from using them.

"Well, probably what we would do is put one of the urine bags on, which I know is usually contaminated because of various things, but that's what we would do." (9, regional PN)

However clinicians who preferred the clean catch method mostly did so because of its lower rate of contamination.

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"I would also explain to them the reason why the clean catch is important is the dilemma of if you get a contaminated specimen you're not sure what you're treating." (1, urban GP)

Some GPs felt that efforts should be made to discourage the use of urine bags, particularly for culture.

"Why are they still making bags for bag urine? If it's not accepted practice… remove the bag altogether because it just gives people the wrong idea." (17, urban GP)

Definitive sample. Collecting a sample that was ultimately likely to be definitive was often considered important. Many clinicians who preferred the clean catch method recognised that urine bags might be helpful for dipstick screening, but felt that urine bag culture would be unreliable due to contamination and false-positives.

"I groan because I think it's only useful when it's negative." (25, rural GP)

Where sample collection was difficult, some GPs might treat empirically for suspected UTI without a confirmatory sample.

"…it's not uncommon for GPs to treat empirically." (13, regional GP registrar)

Clinical progress. Often with time, further clinical information emerged influencing the ongoing need for a sample. Sometimes an alternate clinical focus developed, and some children simply got better with time.

"If the child improves or things like that, and they haven't been able to get it, then I won't see them again. But then obviously the child has improved, and that's ok." (4, urban GP)

Broadly, the barriers and enablers identified by clinicians in this study suggests 4 approaches to urine sample collection in primary care (Table 2). An evidence based approach utilises clean catch for its lower contamination rate. A convenience approach favours urine bags given the time and space limitations of primary care. A pragmatic approach uses clean catch, but also uses urine bags in some circumstances. In rural and remote settings clean catch is used, but catheterisation or SPA is also performed when required for more unwell infants who cannot easily access hospital services.

TABLE 2: APPROACHES TO URINE SAMPLE COLLECTION IN PRIMARY CARE

	Evidence Based
	Use clean catch method Acknowledge can be time-consuming Want to avoid sample contamination

For Review Only

	**Convenience** Use urine bag method Convenience for parent and clinician Aware of sample contamination **Pragmatic** Prefer clean catch Use urine bags sometimes Depends on clinical circumstances **Rural/Remote** Prefer clean catch Not close to hospital services Perform catheterisation or SPA when required

DISCUSSION

Summary

This study explored the barriers and enablers to collecting urine samples from young children in the primary care setting. While intending to identify barriers and enablers to collecting urine samples, what also emerged were how these factors influence the choice of collection method. Clinicians felt in general that collection was difficult and time-consuming, and non-invasive methods were universally preferred.

Barriers to collection included time and space constraints in clinics. Collection attempts were therefore often performed in the home environment by parents. Several enablers for successful sample collection were identified. These included patient hydration, parental motivation and parent education handouts, and the use of voiding stimulation techniques. Invasive methods were rarely performed except in rural and remote areas, and even GPs trained in these procedures felt they were unlikely to be acceptable to parents in an urban primary care setting.

Collection attempts were not always successful. For many children who had improved or an alternate clinical focus had emerged, this was not detrimental, but for others this led to

repeated clinical reviews, untargeted empiric treatment without sample confirmation, or referral to hospital for sample collection.

Strengths and Limitations

The study interviewed GPs and PNs from a diverse range of primary care clinical settings. Clinicians readily engaged with the study topic. Findings provide important insights into how clinicians choose and actually perform urine sample collection within the time, space and resource constraints of primary care. While collection was often performed by parents, this study did not directly interview parents and carers to establish their views, which could also be valuable to inform the relevance and practicality of guideline recommendations.

The lead researcher being a paediatrician was a potential source of bias for the study. As with all qualitative studies, data analysis is subjective and can be influenced by the ideas and assumptions of the researcher. That the research team, which included a GP and a non-clinical researcher, reached consensus on coding and themes arising from the study suggests this was not a limitation to the study. Further, four clinicians were aware that the interviewer had developed the Quick-Wee voiding stimulation technique, but they did not necessarily use the method. Reflexive field notes did not suggest any personal bias influencing the interpretation of results.

Comparison with existing literature

Results are consistent with previous surveys reporting that parents find non-invasive collection time-consuming and difficult, [18 19] and that clinician preferences for collection methods vary. [10 27]

Urine bags are used widely in many countries. [10] Although Australian guidelines recommend against culture of bag samples due to the likelihood of contamination, [7] in this study knowledge about contamination did not deter clinicians from using them.

Clinicians who used voiding stimulation methods found them easy to integrate into practice and acceptable to parents, consistent with previous studies in the emergency department setting. [23 24] Several recent guidelines recommend voiding stimulation techniques such as the Quick-Wee method to improve the speed and success of clean catch collection [7 28-30].

In the Australian and UK healthcare systems, primary care for children is mostly provided by GPs. In other countries such as the USA, it is often provided by paediatricians. This may influence whether invasive collection methods are considered appropriate in the local primary care setting, or recommended in guidelines. [9]

Implications for practice and research

For Review Only

The time, space and resource constraints in primary care strongly influence how clinicians collect urine samples from young children. Non-invasive collection methods are favoured, but current non-invasive methods trade convenience for contamination. All collection methods have advantages and limitations, and there is no single approach suited to every patient and clinical situation. Clinicians must consider factors such as the likelihood of collection success, and the likelihood of collecting an uncontaminated specimen, when choosing the method of sample collection.

The ideal method would be fast, gentle and simple, with low contamination. Further research is needed to optimize the speed, success and contamination of non-invasive collection. Where possible clinicians choosing non-invasive collection should consider voiding stimulation and clean catch, to avoid the higher likelihood of contamination from pad and bag samples.

Some international guidelines recommend the use of invasive collection methods, which may be impractical in primary care in countries like Australia and the UK. Guidelines must consider the primary care context to ensure recommendations are relevant to real-world practice.

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7.8.2 Supplementary table

Table 10: Additional theme and subtheme example quotes

CLINICIAN
Knowledge
Knowledge of contamination of urine bags “The bag urine is heavily contaminated and does not confirm, or rule out the urinary tract infection.” (17, urban GP) “And you can use urine bags, but, my understanding anyway, is that they’re much more prone to contamination. So we try to steer away from those if possible.” (3, urban GP) “I know the bag urines aren't that reliable. If it comes back negative, it's good, but I guess it's hard to rely on a positive” (6, regional GP) “Well, the guidelines for years have indicated that bag urines are inadequate for assessment of, uh, infection in infants and children and also from experience, that the false positives far too high” (24, rural PN) “…the reason why the clean catch is important is the dilemma of if you get a contaminated specimen (with a urine bag) you're not sure what you're treating.” (1, urban GP) “I find that I get very clean samples (with urine bags). And so yeah, I generally don't get any squames or very rarely in my samples, so I'm very happy with the accuracy of it.” (4, urban GP) **Knowledge of contamination of clean catch** “I think that there's less chance of contamination.” (16, regional GP) “I would talk to them about the importance of trying to get a good specimen of urine, and by that a clean catch.” (19, regional GP) “The whole idea of trying to catch something that is mid-stream and trying to reduce contamination is something that is usually pretty familiar to them.” (22, rural GP) “…clean catch still has issues in terms of contamination, and the problems around that.” (2, urban GP registrar) **Knowledge of voiding stimulation methods**

“I've started trying to use saline soaked gauze suprapubically because I read someone did a study that showed that helps speed things along.” (11, urban GP) “…then I would suggest some techniques that I've seen work by this rotating of, um, a wet cloth across the suprapubic region or the flank.” (12, urban GP) “I learned that (voiding stimulation) in my hospital time, where I was doing it. And I think also from the nursing staff. Can't remember, but anyways, it's been quite successful.” (21, urban GP registrar) “…rub the tummy after cleaning and a drink, parents are open to it” (25, rural GP) “…since I learned of the quick-wee method, I have been trying it” (17, urban GP) **Knowledge: of paediatric urine sample collection in general** “I'm just following the guidelines.” (24, rural PN) “We've got local guidelines that are fairly helpful down here. The - what's it called - health pathways.” (8, regional GP registrar) “Well, I can't even remember how you're supposed to do it.” (18, urban GP) “Its hard to know about everything” (17, urban GP)
Training
“I think my GP supervisor when I was training, he did it. And that's where I learnt it.” (14, urban GP) “I learnt that in my post-graduate paediatric training as well as what has been advised on the Royal Children's Hospital website.” (17, urban GP) “I learned that (voiding stimulation) in my hospital time, where I was doing it. And I think also from the nursing staff. Can't remember, but anyways, it's been quite successful.” (21, urban GP registrar) “Probably learnt in my training. In my training, and that was a long time ago. That was the way we always did it” (23, rural PN) “I used to try, because of my training at the children's hospital when I was a young GP, I used to try and always offer suprapubic aspirate because that's what I was trained to do at the children's. I'd probably done about two because parents would rarely look comfortable with you sticking a needle in their child's bladder” (1, urban GP) “I would need further training, I think, because I think I've probably only done one (SPA) in my entire career. So, no, I wouldn't feel ... I'm always worried about perforating the bowel or something. Apparently it's pretty easy in the under twos, but no, I'm not confident.” (8, regional GP registrar) “I worked as a medical educator for The College of GPs and we did do an update for GPs, you know one weekend update, and we decided to do some practical ones and one of the things we did was create a station where they could practice

suprapubic aspirate, so we actually had a little model, we actually made it up, like a little doll and we put a bag inside so that we could simulate where to put the needle and how draw up the urine. And we did that just with probably 30 GPs and I didn't follow up formally, but anecdotally none of them said they were gonna use it in their practice." (1, urban GP)
Experience
"I think I did one once as an intern in ED. Not for a long time." (16, regional GP) "I have not done a suprapubic aspiration for a while now, so I could certainly try, I know the theory behind it, but I have a feeling that I may not be successful. So I think lack of practice, probably would slightly caution me and I'd prefer getting it done by someone with more experienced hands." (17, urban GP) "Yeah, I was taught to do that (SPA) when I was GP registrar and doing a pediatric term and then probably did a few ED patients or babies over the first few years of practice. But I have not done it for a few years." (22, rural GP) "I'd probably ask someone else to do it (catheterisation) just because I'm just not doing a large number of them." (11, urban GP) "If you're doing catheters five times a week, that's quite different from if you're doing one or two a year." (1, urban GP) "Maybe if I had more experience, I might be more inclined to do it." (13, regional GP registrar) "If there's going to be a push to change the way urine is sampled, and perhaps improve the usability of the sample, a suprapubic collection, then I reckon the barrier for somebody like myself, as a registrar, who doesn't have a particular interest in children per se, I think the barrier would be experience." (13, regional GP registrar)
Rurality
"I think in general our rural colleagues do a lot more procedures than we do. Often they are on call for the base hospital, so having that training and experience and expertise would certainly be of value." (17, urban GP) "I imagine I would do it (catheterisation) more if I was in a rural setting." (18, urban GP) "I was in remote Queensland… so I did everything out there" (12, regional GP) "I've become really skilled at doing SPA's now" (19, remote GP) "…when you work in indigenous health and when you work in remote areas it's just not quite the same as when you work in a metro area." (19, remote GP) "…we're remote because our patients have to travel 500 kilometers to get to us, so our cut off for doing certain investigations or doing certain things might be different

to if someone had a hospital around the corner and knew that they could go there in the middle of the night if they got their fever back." (20, remote GP)

"…when I was in a rural area running a little hospital I'd do it (SPAs and catheters) in the emergency department" (5, regional GP)

PATIENT

Age, size, mobility

"And certainly if the child is distressed and uncooperative and won't sit still, that's really tricky. A six month old is clearly easier than a two-year-old because they can't run away from you so the mobility of the child is a factor." (11, urban GP)

"The toddlers are the most difficult. The most, the um, the toddlers that are not particularly unwell, who have a fever, no focus, here, we're talking sort of, 14 months and above who are mobile, walking around, and who won't be voiding very often, it's going to be very difficult." (12, urban GP)

"Catching it mid-stream is very difficult, for instance. So, general contamination of the sample. A difficulty of catching it in a child, because they'd be potentially thrashing about or something like that." (13, regional GP registrar)

"…children often in general practice are not as unwell as in emergency departments, so they are active, they are running around, and that bag just gets thrown on the ground, it gets flung, it gets broken." (2, urban GP registrar)

"…boys do better clean catch samples" (20, remote GP)

Hydration

"…hydration is a very important factor" (21, urban GP registrar)

Hydration as an enabler

"Make sure they're well hydrated." (9, regional PN)

"…the parent really has to make sure that the child's drinking well." (1, urban GP)

"Encourage fluids… It might help produce more urine." (10, regional PN)

"It's quite common to take the nappy off and then within a matter of minutes, have the urine coming if the child is well enough hydrated." (11, urban GP)

Hydration as a barrier

"So not being hydrated, that's a real problem." (11, urban GP)

"Sometimes they're dehydrated, and yeah, they might not wee." (18, urban GP)

"…if they're dehydrated we find it hard to get a sample." (24, rural PN)

"…if they're really dehydrated, you're not going to get much urine out." (8, regional GP registrar)
How unwell the child is
Well enough to wait for a sample "I guess it does depend on the clinical scenario, and if I feel like the child is not unwell, and that we do have further time. We often do get them to just wait, and wait longer." (2, urban GP registrar) "I'd probably start with a urine bag, but that depends on how unwell they are. So if just vomiting, but I thought they weren't septic, then I'd probably just start with a urine bag and see them later on that day or the next day." (5, regional GP) **Need for sample in clinic** "If the child's febrile and there is no focus of infection, whether it's a urinary infection or otherwise, the child could have a significant bacteraemia or brewing something more sinister, I am just not happy to be sending that child home." (22, rural GP) "…you're not going to send a really sick kid home." (8, regional GP registrar) **Need for invasive sampling** "…we might do a catheter if I feel that the child is significantly unwell." (12, urban GP) "If the child is sick, I would do a SPA." (25, rural GP) **Need for invasive sampling in hospital** "If I had a child who was very sick, I'd be weighing up whether I should do that (catheter or SPA), but then if they're that sick I'd be thinking well do they need to be sitting in hospital anyway, do they need a full septic workup." (1, urban GP) "…if the baby was sick enough to require a bladder tap, perhaps they should go into hospital, because they may need further investigations as well." (10, regional PN)
PARENT
Advice provided
Verbal Advice "I would provide them with some verbal instructions on how to collect the urine. I'd also demonstrate how to catch the urine using a, um, a spare urine container and a tap, that I don't want the first part of the urine, and um, I'd also provide them with a handout on how to sample... how to catch the urine." (12, urban GP)

“Generally in my practice I will give brief information about it. So, I'll explain what a clean catch sample is. I'll explain sort of why we're doing it. I'll explain the importance of not putting the container against the genitalia.” (2, urban GP registrar)

“So everything takes longer up there, than probably if it was just in a general practice where English is the first language. So, probably ... I could spend a good five to eight minutes explaining kind of why it's important.” (19, remote GP)

“…mostly parents get it, but you do have to assume that they've got reasonable health literacy” (1, urban GP)

“…it's pretty easy to explain when they piss you wanna catch it in the cup” (20, remote GP)

Written Handouts

“I always provide written instructions. I usually get myself a little piece of paper and then write a few dot points for people. So they don't forget.” (13, regional GP registrar)

“I think I would use that potentially in a scenario where I've gotta send the parent home to collect the specimen. And they might forget what I've said. And then they can go home and they can read it and go through the steps at home. I think that would be useful.” (11, urban GP)

“Yeah and parts of the little diagram as well so they can remind themselves what it should look like when they're trying to catch the urine… I think diagrams are excellent.” (13, regional GP registrar)

“…a one pager that you could print out with some pictures or something like that” (18, urban GP)

“I really liked the idea of the patient information sheet. That's a really good idea.” (9, regional PN)

“We don’t use written instructions.” (25, rural GP)

Motivation

Motivation as a barrier

“…in my experience, parents often say, “Oh, we can't do it,” or “It's too hard.”” (1, urban GP)

“And almost how much emotional resilience the parents have got (to collect a clean catch), to hang around with the urine jar. It really depends on the parents and what they’re up to, and how engaged they are.” (3, urban GP)

“Yeah. Some families are happy to sit there and wait to try and catch a wee. Other families don't feel like that can do that. So I think it's better to get some sample (with a urine bag) rather than nothing. I give them that option as well.” (16, regional GP)

“If I felt like they wouldn't be able to achieve it then it would probably be a futile exercise. So rather than put stress on the parent, I might treat the patient empirically in that event.” (13, regional GP registrar)

“So, yeah, I think in practice, it (clean catch) requires more effort and time from families. So I think that's a barrier.” (17, urban GP)

“…unfortunately at some times it might not be their highest priority to sort out that problem and they might want to get off because the banks gonna shut or something, you know, and getting the sample is not their highest priority and they might not be as keen as we are.” (20, remote GP)

“So clearly some parents are really good at following instructions, you know, "Yes, we've gotta get this done," and others, I don't know, get caught up in other things and might miss the urine or, yeah ... So there's certainly parent factors that can be helpful, make it more difficult.” 11, urban GP)

Motivation as an enabler

“It really depends on the parents and what they’re up to, and how engaged they are… I usually just have a discussion with the parents about those pros and cons, and most people are pretty on board to have a crack at the clean catch.” (3, urban GP)

“…most parents are capable of catching a clean catch” (22, rural GP)

“We've got quite a well educated cohort of patients If I say it's important to have the urine sample, then the urine sample comes back. I haven't had any barriers.” (4, urban GP)

Availability

Parental availability for clean catch

“I can only imagine that, in a parents busy life, the idea of leaving a child without a nappy and tending to it and catching the urine as it comes out is inconvenient, messy.” (14, urban GP)

“…you have to consider all those factors like how many other kids are the parents trying to care for” (1, urban GP)

“…if they've got multiple other kids just the logistics of not being able to be two places at once” (7, regional GP registrar)

“A lot of parents have other children to worry about. I honestly don't know if that (attempting a clean catch) is a practical expectation of a parent.” (13, regional GP registrar)

“For example if there's one parent in charge of three kids and you're telling them sit there, while they're trying to deal with all these other competing demands. So again, the enablers would be that they have two parents available, one to look after the other kids, those kinds of social considerations are probably the big issues.” (1, urban GP)

“I don't think other kids in the household is necessarily a problem” (15, urban GP)

Parental availability to collect at home and return samples

“Working parents or, you know they've got kids in school and they're out and about. Transport. So having to come and drop samples back and things like that can be difficult for people without much money as well.” (16, regional GP)

“I think you gotta fit it for the situation for that particular patient and their family” (10, regional PN)

“…you adapt the process to suit the family that's in front of you” (19, regional GP)

PROCESS

Time

Time constraints in general practice

“…we don't have a lot of time in general practice.” (18, urban GP)

“Logistics in the clinic: time, space, staff” (25, rural GP)

“I think the biggest challenge doing it in the clinic is time and the environment.” (1, urban GP)

“Oh, absolutely. It's time related.” (15, urban GP)

“…time is one of the barriers.” (2, urban GP registrar)

“Parents don’t expect to be waiting around for a long time like at A&E.” (25, rural GP)

“…often it's a time consuming thing of trying to get a sample from an infant it's time the doctors don't have.” (24, rural PN)

Urine bags and time constraints

“Could do either (urine bag or clean catch), but probably with a bag ... anything that takes a little bit of time, we would often ask the nurses to do it to be honest, just to save us a bit of time.” (6, regional GP)

“Probably the, using the bag, simply because, time is often... a bit pressed for time yeah.” (10, regional PN)

Clean catch and time constraints

“Well, it would depend on our space, their timeframe, our timeframe, so probably up to 60 minutes if there was nothing kind of happening, then I would probably give them the option of going home, try and get a clean catch at home or using the urine specimen bag.” (10, regional PN)

“We often do get them to just wait, and wait longer, and get mom or dad depending on the sort of feeding practices, to give the child a drink, whether that's

breastfeeding or giving them a drink... depending on their age, alternatively there's a case of us waiting, and waiting to try and get the sample. If I think it was very important, and I felt we definitely needed to get the sample. We would wait that time, and after that time our nurses are in the treatment room and I am seeing other patients." (2, urban GP registrar)

"…we have it so that it is a pretty flexible sort of practice, so it was no appointment times. I mean, sometimes I would just keep them in my room, or put them in another room and I would kind of go in and out. Just checking in to see how they were. If I felt like they really needed a real hand or assistance, then I would get whoever was available to stay with them then. I think it would then help them go in there. Or myself, if it wasn't easy… So yeah, it's a little bit different from a usual general practice." (19, remote GP)

"So I tend not to do it in clinic as much, particularly because clinic gets quite busy, and then its like if you spend half an hour trying to get a urine sample, the waiting room will be like, why did I do that!" (3, urban GP)

"Yeah, in a pre-continent child, who's going to do that? I mean, you've got to be there at the right time, don't you?" (15, urban GP)

Time constraints and using invasive collection methods

"I think if the way that general practice was run and funded would allow more time for GP's to be able to do these procedures (catheter or SPA) I think people would be more willing. I think with our 15 minute appointment model, having to set up for a procedure and to do a procedure like that will probably take a bit more time, and if that means that it slows us down over the course of the day, I suspect a lot of us would be reluctant to try." (17, urban GP)

Clinic resources

Clinic space

"…practical things, just like having space and equipment." (21, urban GP registrar)

"…every practice is a bit different in terms of its physical environment." (23, rural PN)

"It would depend on the floor plan of the practice I guess." (6, regional GP)

"Having a space where the parent can sit quietly and catch the urine." (12, urban GP)

"So in the practice that I first worked for when I first finished my GP training for 5 years. We sort of had an area, we'd send them into a treatment room." (14, urban GP)

Room availability

"That can be a problem. So, GP clinics are run to make sure that rooms are occupied. So, room availability can be an issue. With the GP, of course, they've got a string of patients that they're expecting. There might be a treatment room or

two associated with the nursing staff. So, if there is a room there that's available, then there might be attempts to do it there." (13, regional GP registrar)

"…in one of the settings I work in because we do have space and it's attached to an emergency department, I would pop them in a second room and just put the baby down and them down and get the jar ready and show the parents what to do and then I might, if it didn't' happen very quickly, then I might leave the parents to sit with the baby." (11, urban GP)

"…we have a number of cubicles in our treatment room, so there is space for us to be able to have a family stay in one area. Potentially up to an hour or two hours if we need them to." (2, urban GP registrar)

Lack of space as barrier to collection in clinic

"Its often very busy and we don't have space or an area to sit a family aside for a clean catch" (10, regional PN)

"I don't think GP's in the community, um, like to, hang on to children, infant in children, and try and see through what's going on. I think they prefer to move on and handball them to a centre that can watch them for a while… They either don't have the space or they don't have the time." (12, urban GP)

"Or you have to have a space to have the baby without the nappy on. You can't just sit them in the waiting room without their nappy on. I mean, you could but we generally choose not to 'cause I think it would put other people off." (11, urban GP)

"…we've only got one treatment room. And it's always booked out with procedures" (21, urban GP registrar)

"I guess it's space, because it's not an option at this clinic. All the rooms are filled with GP or a nurse, every single session. It's very well-run clinic." (21, urban GP registrar)

Nursing staff availability

"In my practice its good because I have skilled nurses who can follow that up, so I can still be seeing other patients while we wait for that sample." (2, urban GP registrar)

"I'm probably lucky that I'm in a position to get some health service staff to help. So there's lots of room and staff to assist the parents in getting a clean catch." (16, regional GP)

"Well potentially, because when I did my first training post at the start last year, there were four nurses and there was quite a large treatment room. And a lot of the GPs had the nursing staff do obs over an hour or they had help from the nursing staff with it so there was kind of more scope. And they had a sort of a ticket system where you give the nurse a ticket and you could continue seeing patients and they'd call them in, so I might entertain it more in a clinic like that." (21, urban GP registrar)

"We often don't have enough nurses" (18, urban GP)

"…perhaps it's something the nurse could do. Having said that, we're not very well staffed with nurses, and the nurse is super busy doing other things." (18, urban GP)

"…the problem with using a practice nurse with this is most of the time I'm seeing children either after hours on the weekend when the nurse isn't there, and even if the nurse was there it takes five minutes to explain it to them, wait for the patient to wait for the nurses probably doing some other task, because these things happen in an ad hoc way, it's not like you've got a nurse sitting there waiting there to step in, having said that our nurses would be very capable of doing it." (1, urban GP)

Convenience of method

Urine bag convenience

"It's probably not the best way to do it, but it's the easiest." (18, urban GP)

"…probably the convenience factor" (10, regional PN)

"Because they're convenient." (12, urban GP)

"Well I guess it's (urine bags) primarily convenient for the parent, time-wise. It's potentially convenient for the clinic because you don't have people staying- waiting to get urines and things like that, which is quite OK in the emergency department, but not necessarily feasible in a general practice." (21, urban GP registrar)

"I actually do like that bag collecting method. I think that's something that's a little easy. You can pop that on a child and perhaps set and forget for a bit, rather than standing there with a cup, hoping and waiting." (13, regional GP registrar)

"…there's a bit of a theme of things that are kind of practical and convenient to do" (13, regional GP registrar)

"Well, it's a convenience for me, but also for the parents you know." (15, urban GP)

"I find that it's actually very convenient" (4, urban GP)

"…the bag obviously is quite straightforward and easy for them" (4, urban GP)

"I just think it is the most convenient" (22, rural GP)

Clean catch convenience

"I guess clean catch would be the most convenient method." (19, remote GP)

Clean catch inconvenience

"You have to put in too much time (for clean catch), either the parent has to be alert the whole time, because I'm not going to hang around and do it" (15, urban GP)

"I guess what I mean by that is that I perceive that you've gotta be pretty lucky to have this sort of ... to be there, no nappy on, lying down, the jar next to you, and you get a spurt. And they might, yes; The fact that really my three daughters nearly

never wee'd on me when I changed their nappies so ... yeah ... there's be a bit of waiting around here to get a sample and you might not get it; the moment the parent turns away, is the moment they wee or something. That would be my perception or my bias if you like, about why doing that sort of a clean catch is not practical." (6, regional GP)

"…the problem that parents report is when they go home and they try and do it, often find it's not that easy" (1, urban GP)

"And clean catch, I don't know. We might've done it once ages ago, but it would be hard." (18, urban GP)

"I've heard people standing there and waiting for some wee to come out and the parents trying to catch it in a cup. I don't know how realistic that is." (13, urban GP registrar)

Likely speed and success

Clean catch: speed

"The downside of a clean catch is that it often takes a little bit more time to collect. It takes a bit of patience." (11, urban GP)

"Its (clean catch) very time-consuming." (13, regional GP registrar)

"I think it's (clean catch) an excellent method, but it's obviously very time consuming." (4, urban GP)

"Well, it depends how well it works and how long it takes... because we don't have a lot of time in general practice" (18, urban GP)

"So I tell the parents it's gonna take, anything from a few minutes, to, two or three hours." (12, urban GP)

"…sometimes if families have been waiting around with other kids, they can get a little impatient" (2, urban GP registrar)

Clean catch: success

"…a clean catch is nearly impossible ... fluky if you can do it" (6, regional GP)

"I would always try (clean catch) in the clinic first and you know, you might get lucky. But then you have to pull the pin for a bit at some point, depending on who's available at the time, what kind of time can we devote to doing it. You know, if it's a quiet time for a nurse or myself, we'd probably give it a go or at least demonstrate what we're trying to achieve." (13, regional GP registrar)

"It depends how it works. If it was reliable and it worked right away, I could do it." (18, urban GP)

Urine bag: success

"It is just difficult to get those urine bags to work, difficult to apply, difficult to get a clean sample. So I'm not sure what the percentage would be, but lots of the time

the parent comes back and says it's just leaked and they haven't been able to get anything.” (5, regional GP)

Likely speed and success: voiding stimulation

Clinicians using voiding stimulation methods

“I've started trying to use saline soaked gauze suprapubically because I read someone did a study that showed that helps speed things along.” (11, urban GP)

“Rub the tummy after cleaning and a drink, the parents are open to it.” (25, rural GP)

“…since I learned of the quick-wee method, I have been trying it” (17, urban GP)

“Gentle massage of their back and tummy just very gentle, yeah so all of those things we'd try to use to perhaps get someone to urinate.” (24, rural PN)

“I suppose the Quick-Wee method kind of gives you more confidence in being able to get that sample” (3, urban GP)

Clinicians open to using voiding stimulation methods

“I think they would be very open for that. I mean ultimately we would want to get a sample of urine and if that's going to help, if there is a trigger that's, you know, not harmful to the child, straight forward, easy, yeah definitely do it.” (10, regional PN)

“Definitely. If there were sort of practical, simple things that would make it easier to collect. Yes, I would be very keen to try that.” (19, remote GP)

“So that would be much better if we could press a button and make urine.” (5, regional GP)

Invasiveness

Parental acceptance of invasive collection procedures

“…parents would rarely look comfortable with you sticking a needle in their child's bladder, even if we tell them that it's quite safe” (1, urban GP)

“I think a lot of parents would not feel that happy about me sticking a needle in their child's stomach. I would be reluctant.” (18, urban GP)

“I think the idea of a percutaneous intervention for an infant or baby is quite intimidating for a parent. They may not understand the relevance or appreciate the significance of it in a general practice setting, but in the Hospital setting where there is generally a higher acuity of pathology, I think parents are more accepting of the need to undergo such a procedure.” (17, urban GP)

“I mean the more invasive it is, the more difficult it is to sort of get consent, and there's families that won't let you do a catheter, let alone an SPA” (20, remote GP)

Pain and distress for the child

“there's the impression that it's well it's not a pleasant thing to do, it's really invasive, it's a bit of a nasty thing to do” (5, regional GP)

“Yeah, and I prefer not to do that upfront because well I have reasonably good success at getting clean catches with the help of parents and I realize that it is a bit more traumatic for the child and so it's not as nice, that's all.” (11, urban GP)

Risk of complications

“Well the pro is that you get a much cleaner collection. The con is, I have images of needles going through the bowel.” (15, urban GP)

“There is more the risk of bowel perforation or again you have got pain, and it can be quite traumatic. It is all about being concerned about going in the wrong place really.” (22, rural GP)

Non-invasive collection methods in the GP setting

“I think anything that is non-invasive” (19, remote GP)

“Because it's (urine bag) less invasive than the other options” (5, regional GP)

“Absolutely if it wasn't invasive or um you know, I think if it's non invasive and it's not gonna do anymore harm absolutely.” (24, rural PN)

“Not invasive (clean catch), not scary for parents.” (19, remote GP)

“On the scale of things it's (voiding stimulation) the least invasive that we could be doing.” (21, urban GP registrar)

Invasive procedures in the GP setting

“…the invasive nature of the procedure… is the barrier” (13, regional GP registrar)

“I just think they're (SPA and catheter) invasive and not necessary” (4, urban GP)

Invasive procedures in the hospital setting

“I am aware of attempting to obtain a suprapubic urine sample, but I tend to avoid that in general practice because if a child is that sick, that requires an invasive way of having urine, the urine sample should be done in hospital.” (17, urban GP)

“…a bit traumatic as well, more likely if the child is unwell rather than well” (22, rural GP)

Collect in clinic or go home

Collection at home

“They'd go home, I mean you've got to wait for the child to urinate.” (15, urban GP)

“Yeah, so if it's something that the family can do at home and we don't have the time, I suppose that's a time saver for us and reasonable request.” (16, regional GP)

“Always at home, firstly because our clinic only has one bathroom facility, so to attempt to obtain a urine sample from a baby may take a bit time and that would utilize the one bathroom that we have. Second of all I think most parents want to be given the opportunity to try to do the collection in a more relaxed setting, make the child a little bit more at ease.” (17, urban GP)

“…well in our particular practice, we'll encourage them to catch the urine at home” (12, urban GP)

“Occasionally (at home), but it never works. You send home urine jars and they never come back.” (20, remote GP)

Collection in clinic

“Usually we encourage them to do it in the practice.” (23, rural PN)

“I would always try in the clinic first and you know, you might get lucky. But then you have to pull the pin at some point.” (13, regional GP registrar)

“If we can do it by ourselves on site, then the return rate is higher.” (14, urban GP)

“…they might try for a little bit here and then go home and keep trying” (5, regional GP)

“Occasionally (in clinic). Not really though. Because this is community medicine. The vast majority of our patients live within, and its inner metro as well, people essentially live within 5 minutes walk. So it’s a lot easier for people to go home.” (3, urban GP)

“…really doing it in the clinic is quite challenging” (1, urban GP)

OUTCOME

Contamination

Contamination collecting urine samples in general

“Contamination, you get a bug, but you don't know if it's the right bug because of contamination.” (20, remote GP)

“I think contamination is always a problem with urine samples, even with adults” (24, rural PN)

“…it's really important to get sterile specimen because otherwise you could end up inappropriately treating something that you don't need to treat or not knowing what you are treating” (1, urban GP)

“…you've sort of lost the opportunity to discover potentially whether it was a UTI that was resistant to the antibiotics. Or just not a UTI to begin with at all.” (19, remote GP)

Contamination of urine bags

"…that's how I found out how crap bags were because I always get a contaminated specimen" (1, urban GP)

"…bag urine is often contaminated" (18, urban GP)

"…it's (urine bag sample) really highly likely to be contaminated. And I cannot send that specimen to the lab for a culture" (11, urban GP)

"So if I can't send it (urine bag sample) for an MCS, then I can only use it to do a urine dipstick and I can't really rely on the urine dipstick result so I figure why waste my time." (11, urban GP)

"…there's higher rates of contamination, with that because of the bag being attached to the skin" (2, urban GP registrar)

"Well, probably what we would do is put one of the urine bags on, which I know is usually contaminated because of various things, but that's what we would do." (9, regional PN)

"I find that I get very clean samples. And so yeah, I generally don't get any squames or very rarely in my samples, so I'm very happy with the accuracy of it." (4, urban GP)

Contamination of other methods

"I think that the pad rate, probably has a higher rate of contamination than the other methods. I think a clean catch and a suprapubic, certainly, have lower rates of contamination. And the other ways of collecting, because I've not used them, I wouldn't know. I would suspect that they are also a lower rate of contamination." (14, urban GP)

"I think that there's less chance of contamination (with clean catch)." (16, regional GP)

Definitive sample

"I'm following, well, the guidelines for years have indicated that bag urines are inadequate for assessment of, uh, infection in infants and children and also from experience, that the false positive's far too high" (12, urban GP)

"I usually get them to do two samples, as well. So there might be a better chance of picking up if there is really something on there" (14, urban GP)

"…the bag urine is heavily contaminated and does not confirm, or rule out the urinary tract infection" (17, urban GP)

"So it's (bag urine) potentially going to miss the diagnosis of the UTI, which is going to confuse the picture in terms of knowing how long to treat, knowing whether to investigate more, knowing whether if they truly have a UTI." (19, remote GP)

"…when I first trained back in the ninety's there was still a practice of collecting some bag urine back then. They were pretty much only useful if they came back negative" (22, rural GP)

"I know the bag urines aren't that reliable. If it comes back negative, it's good, but I guess it's hard to rely on a positive" (6, regional GP)

"And then the trade off is that you need to be much more vigilant with a catch, you get a better sample but its harder to get." (3, urban GP)

Clinical progress

Improvement in clinical condition

"No. If the child improves or things like that, or they haven't been able to get it, then I won't see them again. But then obviously the child has improved, and that's ok." (4, urban GP)

"Generally, if I give the parents a bottle and tell them to get a clean catch with the baby's nappy off. I just don't see the sample back in the clinic. So, there's no result and you ring them up and they go, "Oh, they explain the child is better." So there is no sample done." (14, urban GP)

"I've found most parents have come back with something. Either with something or with a well child and in which case I'm sort of happy." (7, regional GP registrar)

Deterioration in clinical condition

"The risk with that of course is if the child deteriorating over night, they might become more dehydrated, then you might have trouble getting urine specimen, but I guess then in that case it becomes a different kind of problem, you're gonna have to send them to hospital for further assessment." (1, urban GP)

"Or I guess they may have also been circumstances where the child has been referred to the emergency department or something, if the child has deteriorated and they weren't able to get the sample, or something like that." (4, urban GP)

"…we would tell them if the child gets unwell overnight, go to the ED." (9, regional PN)

Develop alternate focus

"Sometimes what happens is you try to give the urine container and get the clean catch and then they can't do it but they come back with the patient and either you re-examine them and the fevers gone or they've developed a cough or something like that so another focus becomes clear" (3, urban GP)

"So if the child was getting better or a focus had become more obvious then I probably wouldn't pursue it, but if the child was still sick or getting worse then I'd send them somewhere else." (5, regional GP)

"With that said, I do have a lot of patients who do develop a focus of infection subsequently and the parents no longer try, so, I do warn them, as part of my preamble, that if they, for example, develop a respiratory focus down the track,

with a fever, then that's the most likely source of the infection, and therefore we can forgo catching a urine sample. However, if a child is febrile without a source at the 48 hour time point, I would still ask them to come back for review anyway." (17, urban GP)

7.9 DISCUSSION

The main discussion is included in the article in press paper, with additional discussion critically evaluating the research included in this section.

7.9.1 Subjectivity

Qualitative research is by its nature a subjective process, with the researcher bringing their own assumptions and perspectives into the research. [294]

The doctoral candidate being a paediatrician had the potential to introduce bias into the interview process. For example, approaching interviews with pre-conceived assumptions of expertise could alter discussion.

This risk of bias was considered in advance through careful formulation of the interview guide and schedule. These were reviewed and refined with the other members of the research team, which included an experienced GP and an experienced non-clinical researcher who both have extensive qualitative research experience. Non-judgemental language and open questions were used to minimise bias, such as the preface to the clinical scenario:

"I'm going to ask a few questions about a clinical scenario. It's not a test, and there are no right or wrong responses. I'm just genuinely interested in your answers."

Interview questions were initially tested with the other members of the research team. The interview schedule was then piloted face to face with two GPs: one GP trainee registrar and one experienced GP. They were asked to provide any feedback they felt relevant about the interview questions and

style, and specifically if there were any questions or ways in which questions were asked that they felt may have influenced the way they responded. No issues were identified.

7.9.2 Reflexivity

The research process was also considered through a process of reflexivity, which involves critical reflection on the knowledge produced and the researcher's role in producing that knowledge. Reflexivity is a form of "quality control" for qualitative research, [294] and is a standard part of reporting guidelines for qualitative studies. [289 290]

7.9.2.1 Functional reflexivity

Functional reflexivity is the process of paying critical attention to the way research tools and processes could have influenced the research. [294]

The method of data collection in this study was interviews conducted face to face or by telephone. These methods seemed appropriate given the general clinical nature of the research topic. On reflection, conducting interviews with participants in their own clinical settings was felt to positively facilitate a connection with the clinical subject matter.

7.9.2.2 Personal reflexivity: role as a paediatrician

Personal reflexivity is the process of bringing the researcher into the research, as a visible and present part of the qualitative research process. [294]

Field notes were documented after each interview, and these specifically considered any impressions and reflections of how being a paediatrician could have influenced the interview process. This did not identify any undue influences, suggesting that the proactive consideration given to developing the interview schedule and piloting questions was an effective strategy.

A small majority of participants reported preferring the clean catch method, with a large minority preferring urine bags, and one participant preferring

cotton wool balls. This diversity of preferred collection methods suggests that participants felt able to answer interview questions openly and honestly.

Most participants who preferred urine bags were aware of the high risk of contamination of these samples, but this was openly reported, suggesting the participants were not influenced by the knowledge that the doctoral candidate conducting the interview was a paediatrician.

"Well, probably what we would do is put one of the urine bags on, which I know is usually contaminated because of various things, but that's what we would do." (9, regional PN)

As described in the discussion of the article in press paper, the research team (which included an experienced GP and an experienced non-clinical researcher) reached consensus on the coding and themes in the study, suggesting that the doctoral candidates professional background as a paediatrician did not bias the analysis and study results.

7.9.2.3 Personal reflexivity: role having developed the Quick-Wee voiding stimulation method

The use of voiding stimulation methods was included as a potential prompt in the final section of the interview schedule (Figure 28). This included both the bladder-lumbar stimulation method, [234] and the Quick-Wee method. [251]

Figure 28: Interview schedule, specific collection methods

What's The Catch Interview Schedule

Section 6: Specific collection methods

6 Can you tell me what you think about other collection methods?

PROMPTS
+ urine collection bags
+ clean catch
+ voiding stimulation methods (like lumbar/bladder stimulation or Quick-Wee)
+ catheterisation
+ suprapubic needle aspiration

+ what are the pros and cons of that method
+ do you ever use that method in your practice

In the interviews, several clinicians reported using the Quick-Wee voiding stimulation method, but did not know the method had been developed by the interviewer.

"I've started trying to use saline soaked gauze suprapubically because I read someone did a study that showed that helps speed things along." (11, urban GP)

"I learned that (voiding stimulation) in my hospital time, where I was doing it. And I think also from the nursing staff. Can't remember, but anyways, it's been quite successful." (21, urban GP registrar)

Four clinicians were aware that the interviewer had personally developed the Quick-Wee voiding stimulation technique, however only two of the clinicians who knew this actually used the method.

7.9.2.4 Reflexivity: summary

In summary, the doctoral candidate used reflexivity to consider how his place within the research as a paediatrician impacted the knowledge generated by

the study. Critical reflection suggested it did not unduly influence research processes and findings.

7.9.3 Generalisability

This study was conducted in the Australian primary care setting.

Findings may be of interest for countries with similar primary care settings in terms of government subsidised services and health workforce training, such as the UK and New Zealand.

Some of the barriers and enablers identified may be relevant to GPs, primary care nurses and family physicians in other countries with different health service structures and workforces.

7.9.4 Implications for practice and further research

7.9.4.1 Practical and convenient non-invasive collection methods

The study findings highlight the need for simple, quick and effective urine sample collection methods suitable for use in the primary care setting. Non-invasive collection methods were universally favoured by the GPs and PNs participating in this study. Collection methods must be practical and convenient to use within the time and space constraints of primary care.

7.9.4.2 Reducing contamination of non-invasive collection methods

Primary care clinicians had good knowledge of the risk of contamination of non-invasive collection methods. However despite knowing that urine bags have the highest contamination of all collection methods, they were favoured by many clinicians for their convenience. Further research is required to reduce the contamination of non-invasive collection methods.

7.9.4.3 Enabling resources for parental collection

Parents often carried out urine sample collection for young children in primary care, whether in the clinic itself or at home. Parental motivation, and

understanding why collecting a sample was important, were identified as enabling factors. Written parent education handouts incorporating diagrams and visual instructions were suggested as an important resource to enable successful sample collection.

7.9.4.4 Knowledge of voiding stimulation methods

Clinicians' knowledge of voiding stimulation methods was variable in this study. However GPs who used voiding stimulation felt it was easily incorporated into their clinical practice, and highly acceptable to parents. GPs and PNs who were not aware of voiding stimulation methods were open to trying them. This suggests the need for ongoing knowledge translation efforts to promote the use of voiding stimulation methods in primary care.

7.10 CHAPTER SUMMARY

The main aim of this chapter was to explore and characterise the barriers and enablers to collecting urine samples from young pre-continent children in the Australian primary care setting. What also emerged was how these factors influence the clinician's choice of collection method.

Non-invasive collection methods were strongly favoured by Australian primary care clinicians participating in this qualitative study, though clinicians felt in general that non-invasive methods could be time-consuming and not always successful. Current non-invasive methods trade convenience for contamination, and most clinicians were aware of the high contamination rate of bag urine samples.

Invasive collection methods were not favoured, and were considered more suited to acutely unwell children in the ED or hospital, or in the rural and remote clinical setting. Even GPs trained to perform these procedures felt they were unlikely to be acceptable to most parents in the urban primary care setting.

Barriers to collection included the time and space constraints of the clinic environment, and therefore samples were often collected by parents at home. Enablers for successful collection included optimising hydration, parental motivation and education resources, and the use of voiding stimulation techniques such as the Quick-Wee method.

There is no single approach suited to every patient and clinical situation, therefore clinicians must consider factors including the likelihood of collection success, and likelihood of sample contamination, when choosing the method of sample collection.

These study findings inform Chapter 8 of the thesis, which describes the knowledge translation plan for the Quick-Wee voiding stimulation method. Paper 8 specifically includes a parent/caregiver handout as a supplementary file, as this was identified as an important enabler in this chapter.

The implications of these study findings for policy, practice and future research are further discussed in Chapter 9.

Chapter 8 KNOWLEDGE TRANSLATION

"Knowledge derived from research and experience may be of little value unless it is put into practice."

World Health Organization (2012) [295]

8.1 OVERVIEW

This chapter describes part 8 of the thesis, the knowledge translation plan.

Sections 8.2 – 8.6 includes the rationale, aims and methods.

Sections 8.7 – 8.8 describes and discusses the knowledge translation outputs.

PAPERS 7-9: CLINICAL REVIEW PAPERS

The following published papers (Papers 7-9) arising from this chapter are included in the appendices of this thesis:

7. **Kaufman J.** How to… collect urine samples from young children. *Archives of Disease in Childhood Education & Practice*, Published Online First: 23 August 2019. doi: 10.1136/archdischild-2019-317237

8. **Kaufman J**, Temple-Smith M, Sanci L. Urine sample collection from young pre-continent children. Common methods and the new Quick-Wee technique. *British Journal of General Practice* 2020; 70 (690): 42-43. doi: 10.3399/bjgp20X707705

9. **Kaufman J**, Tosif S, Duke T. Voiding stimulation methods for collecting urine from young pre-continent children [Letter to the editor] *Paediatrics and International Child Health*, 2017; 37(4), pp. 298–299. doi: 10.1080/20469047.2017.1399650

The doctoral candidate conceptualised and initiated each of these articles, and wrote the first and final drafts of each manuscript, which were reviewed by all co-authors.

8.2 RATIONALE

The overall aim of this thesis was to optimise the investigation of UTIs in young pre-continent children, by overcoming the existing challenges of non-invasive urine sample collection.

Chapters 4 and 5 of this thesis describe the new Quick-Wee voiding stimulation method, and comprehensive evidence demonstrating effectiveness and acceptability. Chapter 6 provides evidence for superior cost-effectiveness compared to other non-invasive collection methods, and the costs of all collection methods. Chapter 7 identifies the barriers and enablers for sample collection in the primary care setting, with voiding stimulation methods such as Quick-Wee identified as an enabling strategy. These studies have been published in prominent journals.

However undertaking and disseminating research does not automatically see findings translated into practice, policy and guidelines. Much research fails to influence practice or policy, or takes a decade or more to do so. [296]

The importance of translating research into practice is acknowledged by the Australian National Health and Medical Research Council (NHMRC):

"The creation of knowledge does not, of itself, lead to widespread implementation and positive impacts on health. The knowledge must be translated into changes in practice and policy for the benefits to flow to Australians." [297]

As such, targeted efforts are required to translate the knowledge generated from the preceding doctoral research into improved clinical care for young children.

8.3 BACKGROUND

The aim of research is to generate new knowledge and evidence. Knowledge translation (KT) is an emerging paradigm to ensure the use of knowledge and evidence, and address the many challenges of putting research into practice.

The World Health Organization (WHO) defines KT as:

"the synthesis, exchange, and application of knowledge by relevant stakeholders to accelerate the benefits of global and local innovation in strengthening health systems and improving people's health." [295]

KT has other definitions and is referred to under various terms and guises in the literature. KT encompasses many theories, frameworks, models, activities and tools. There is no single KT theory or framework that fits all projects.

For the purposes of this thesis chapter, KT is considered as:

"the process of raising awareness of knowledge and facilitating its use". [298]

8.4 AIMS

8.4.1.1 Primary Aim

The primary aim of this knowledge translation plan was:

I. Incorporation of the Quick-Wee method into clinical practice guideline recommendations.

8.4.1.2 Secondary Aims

Secondary aims of this knowledge translation plan were to:

II. Raise awareness of the Quick-Wee method amongst parents, caregivers, clinicians, researchers and policy makers.

III. Produce targeted education resources to facilitate use and uptake of the Quick-Wee method within key specialty groups.

8.5 RATIONALE

Disseminating the preceding research findings into a broad range of clinical and policy settings will facilitate knowledge translation.

8.6 METHODS

Many different theories, models and frameworks for KT exist, [299] giving rise to a myriad of potential KT activities. Many of these were not within the scope of this doctoral research.

However KT is increasingly recognised as a vital component of research. Therefore a pragmatic approach was adopted to maximise impact within the time and resources available. Key users included parents, caregivers, clinicians, researchers and policy makers. The KT plan was developed opportunistically and adapted as studies from this thesis were published. No specific framework was adopted.

Methods to produce direct outputs targeting key users included:

I. Revision of the Victorian statewide UTI clinical practice guideline.
II. Targeted consumer education resources for clinicians and caregivers.
III. Targeted clinical review article publications to highlight the clinical utility of the new Quick-Wee method.

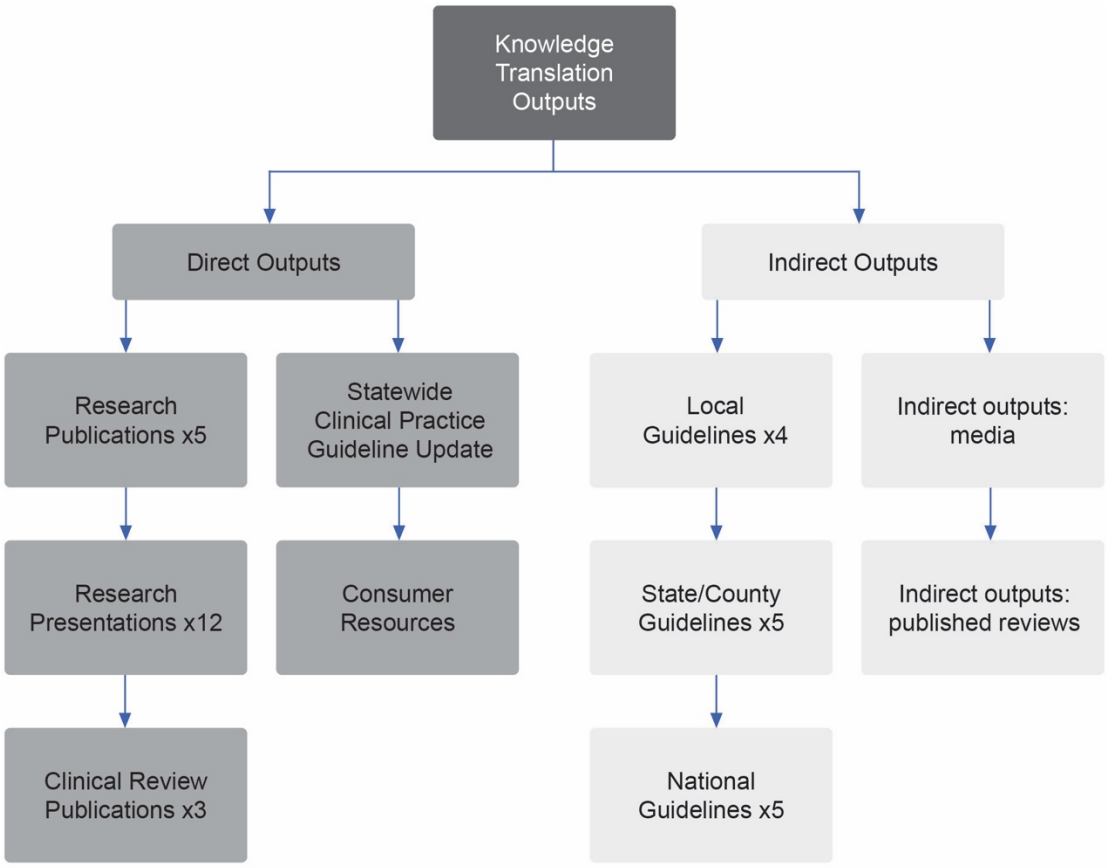
KT plans commonly include both outputs and an outcome evaluation. Outputs, which can be both direct and indirect (Figure 29), are what is produced from the research activities. [298] Outcomes are the immediate, intermediate and long term results and consequences of the research. These include awareness of the research, successful implementation of the

research, and incorporation of new evidence into guidelines, policies and clinical practice. [299]

A formal outcome evaluation was beyond the capacity of this doctoral thesis. Some data was collected with a focused scoping process for the inclusion of the Quick-Wee method into clinical practice guidelines, as this was felt to be an important measure of KT for this research. The scoping process utilised basic web searches supplemented by personal correspondence received from colleagues, clinicians and researchers.

8.7 RESULTS

Figure 29: Knowledge translation overview of outputs



8.7.1 Direct outputs: research publications & presentations

Direct research outputs included:

- 5 research publications (Papers 2-6, included in previous chapters)
- 12 national and international conference presentations (see Preface)

These publications and presentations targeted clinicians, researchers and policy makers.

8.7.2 Direct outputs: clinical review articles

Further direct outputs targeting key specialty groups included:

- 3 clinical review articles (Papers 7-9)

The review articles about urine sample collection in young children were designed to target clinicians in specific settings. These place the research in context of existing practice in these settings, with targeted supplementary resources to encourage translation into practice.

This is in addition to the clinical review article providing a general overview of paediatric UTI, included previously in Chapter 2 (Paper 1).

Paper 1 and Papers 7-9 are available in Appendix 11.1, with hyperlinks to the papers and supplementary files included below (Table 11).

Table 11: Direct KT outputs - clinical review articles

PAEDIATRIC & PAEDIATRIC EMERGENCY CLINICIANS
PAPER 7 Kaufman J. How to… collect urine samples from young children. *Archives of Disease in Childhood Education & Practice*, Published Online First: 23 August 2019. doi: 10.1136/archdischild-2019-317237 **SUMMARY** Article reviews each urine sample collection method including voiding stimulation, and describes collection procedures, indications, and strategies to optimise success and reduce contamination. Includes summary of international guideline recommendations for collection methods. **SUPPLEMENTARY RESOURCES** Online supplementary video demonstrating how to perform the Quick-Wee method, which can be used as an educational resource for departmental education and training sessions.
PRIMARY CARE CLINICIANS
PAPER 8 Kaufman J, Temple-Smith M, Sanci L. Urine sample collection from young pre-continent children: common methods and the new Quick-Wee technique. *British Journal of General Practice*, 2020; 70: 42–43. doi: 10.3399/bjgp20X707705 **SUMMARY** Overview of common urine sample collection methods used for young pre-continent children in primary care, including use of voiding stimulation techniques. **SUPPLEMENTARY RESOURCES** Parent/carer handout for collecting clean catch urine samples and using the Quick-Wee method. Design of handout informed by preceding qualitative study.
CLINICIANS IN RESOURCE LIMITED SETTINGS
PAPER 9 Kaufman J, Tosif S, Duke T. Voiding stimulation methods for collecting urine from young pre-continent children. [Letter to the Editor]. *Paediatrics and International Child Health* 2017 Nov 21:1-2. doi: 10.1080/20469047.2017.1399650 **SUMMARY** Highlights benefits of voiding stimulation techniques for urine sampling from young children in resource-limited settings. Summarises both Quick-Wee and bladder-lumbar stimulation methods as pragmatic ways of improving clean catch collection that require minimal resources.

8.7.3 Direct outputs: Victorian statewide paediatric UTI guideline

Local and state guideline recommendations for urine sample collection methods are provided by the Royal Children's Hospital (RCH) and statewide Victorian clinical practice guidelines (CPGs). The CPGs target clinicians as the intended users.

The doctoral candidate led the 2017 Paediatric UTI CPG update and wrote the first draft of the updated CPG, with input and supervision from A/Prof Mike Starr (paediatrician and CPG Group Convenor). Members of the CPG group provided further feedback and suggestions, which were incorporated for review at the CPG Development Group monthly meeting. The doctoral candidate then wrote the final version of the updated guideline.

Table 12: Direct KT outputs - Victorian clinical practice guideline

CLINICAL PRACTICE GUIDELINE: ROYAL CHILDREN'S HOSPITAL/ VICTORIAN STATEWIDE
OVERVIEW OF THE GUIDELINE The RCH is the major tertiary paediatric centre in Victoria and is Australia's largest paediatric hospital. The RCH CPGs are widely used in Australia and internationally by clinicians in primary care, paediatrics and emergency medicine, accessed via the RCH website and CPG smartphone app with over 4.5 million page views annually. Several guidelines including this one become formally adopted by the Victorian Paediatric Clinical Network as statewide CPGs. For some conditions like paediatric UTI where national guidelines do not exist, the RCH CPGs are often used and cited as de facto national guidelines. **SUMMARY** The CPG provides endorsed local and statewide recommendations for the assessment and management of paediatric UTI. For urine sample collection, the CPG recommends clean catch collection for pre-continent children who are not too unwell, and now recommends use of the Quick-Wee method to improve the yield of clean catch attempts. https://www.rch.org.au/clinicalguide/guideline_index/Urinary_tract_infection/

8.7.4 Direct outputs: kids health information fact sheets

To complement the CPG update, the doctoral candidate also updated two RCH kids health information (KHI) fact sheets, for paediatric UTI and

paediatric urine samples. The fact sheets targeted parents and carers as the intended user group, showing how to perform the Quick-Wee method using a simple “clean, rub, catch” 3-step process

The doctoral candidate led the fact sheet update and wrote the first draft with input from A/Prof Mike Starr (paediatrician) and Ms Amber Ledsam (RCH Community Information Manager). Members of the KHI Committee then provided further feedback and suggestions, which the doctoral candidate incorporated to write the final version.

Table 13: Direct KT outputs – kids health information fact sheets

KIDS HEALTH INFORMATION FACT SHEET: PAEDIATRIC URINE SAMPLES
OVERVIEW OF THE FACT SHEETS RCH KHI fact sheets provide information for families about common medical conditions of childhood. They are widely used by hospital and community health professionals as an educational resource, and also directly accessed by the public via the RCH website and KHI smartphone app with over 8 million page views annually. **SUMMARY** The fact sheet describes each method of collecting urine samples from children. The fact sheet outlines instructions for how to perform the recommended clean catch method, with Quick-Wee voiding stimulation. This includes a simple 3 step “clean, rub, catch” process, with illustrations from the original BMJ publication adapted by the doctoral candidate and Mr Bill Reid, RCH Creative Studio. https://www.rch.org.au/kidsinfo/fact_sheets/Urine_samples/
KIDS HEALTH INFORMATION FACT SHEET: PAEDIATRIC UTI
OVERVIEW As above. **SUMMARY** The fact sheet provides an overview of UTI in children explained in lay terms for parents and carers, and links to the subsequent fact sheet on urine samples (see below). https://www.rch.org.au/kidsinfo/fact_sheets/Urinary_tract_infection_UTI/

8.7.5 Indirect outputs

As well as the direct outputs described above, additional indirect outputs further contributed to knowledge transfer to target users. Each group of users

required different targeted avenues of communication, for example ED doctors would be unlikely to frequently read GP journals. Table 20 in Appendix 11.8 summarises these indirect outputs for different groups of users, including published reviews and media mentions.

8.7.6 Main outcome: inclusion in guidelines

Inclusion in clinical practice guidelines was considered an important knowledge translation outcome.

Fourteen guidelines recommending the Quick-Wee method at either local hospital, state or national level were identified. These guidelines were found via the scoping process described previously in section 8.7.1 (as of December 2019) and are listed in Table 14.

Table 14: Guideline outcomes

LOCAL HOSPITAL & HOSPITAL NETWORK GUIDELINES
1. Australia: Royal Children's Hospital, UTI Clinical Practice Guideline* (2017) [16]
2. UK: Great Ormond Street Hospital, Specimen Collection Guideline (2017) [300]
3. US: Northern California Pediatric Hospital Medicine Consortium: Pediatric UTI Guideline (2018) [301]
4. Canada: Charles Lemoyne Hospital: Pediatric UTI ED Departmental Guideline (2018) [302]
STATE/COUNTY GUIDELINES
5. Australia (Victoria): Statewide UTI Clinical Practice Guideline* (2017) [16]
6. Australia (Queensland): Queensland Health: UTI Management in Children Guideline (2019) [269]
7. Australia (Queensland): Queensland Government Primary Care Clinical Manual (2019) [274]
8. UK (Wessex): Empiric Antibiotic Guidelines for Children, UTI (2018) [303]
9. UK (North Hampshire): Guidelines for Antibiotic Prescribing in the Community (2018) [304]
NATIONAL/INTERNATIONAL GUIDELINES
10. UK: Public Health England Diagnosis of UTI: Quick Reference Tool For Primary Care (2019) [305]
11. Canada: Trekk Paediatric Emergency Medicine UTI National Guideline (2019) [306]
12. Finland: UTI Current Care Guideline (2019) [259]
13. Italy: Febrile UTI in Young Children Guideline (2019) [104]
14. Netherlands: Dutch Association for Urology: Urinary Tract Infection in Children Guideline (2019) [307]

* same guideline: RCH and statewide Victorian guideline

Further translation may continue to occur as other guidelines are updated in the future. While guidelines do not necessarily change practice in and of themselves, they are an important step in the process of uptake and knowledge translation. [308]

8.8 DISCUSSION

The main aim of the KT plan and this chapter was the incorporation of the Quick-Wee method into clinical practice guideline recommendations. The KT plan also aimed to raise awareness of the Quick-Wee method internationally, and produce targeted resources to facilitate use of the method.

Although the implementation of a formal plan was beyond the scope of this doctoral research project, a limited plan was attempted as described in this chapter.

Outputs generated included:

- 5 research publications [246 251 254 272 309]
- 4 clinical review publications [20 132 192 310]
- 12 conference presentations
- education handout and video published as supplemental journal files
- 2 consumer fact sheets produced for the Royal Children's Hospital

Inclusion in clinical practice guidelines was considered an important KT outcome, as a logical proxy measure for use of the method. In a 2 year timeframe since publication of the RCT, the Quick-Wee method features in 14 guidelines from 7 countries, including:

- 4 hospital guidelines [16 300-302]
- 5 state/county guidelines [16 269 274 303 304]
- 5 national/international guidelines [104 259 305-307]

8.9 CHAPTER SUMMARY

The work described in this chapter has started the knowledge translation process, and is an important step in the knowledge translation journey for this doctoral research. Some of the knowledge generated has already been translated into clinical practice guidelines across a range of settings, demonstrating the impact of this research.

Chapter 9 DISCUSSION

"A simple method of suprapubic stimulation with cold water can improve the chances of an infant voiding within 5 min and those of successfully catching a sample. This could easily be introduced into busy emergency departments with staff requiring little training or resources. It would likely hasten the time taken to see, investigate and treat some infants who are suspected of having a urinary tract infection."

Ray & Forbes (2017) [311]

9.1 REVIEW OF CONTEXT AND PROBLEM STATEMENT

UTIs are one of the commonest bacterial infections of early childhood. Clinical signs are non-specific, and many UTIs in young children are missed on initial presentation. [41] If untreated, UTI can cause serious complications including sepsis and permanent renal scarring. Guidelines therefore recommend all young children with suspected UTI or unexplained fever have a urine sample tested, which is mandatory to diagnose or exclude UTI. [20]

The problem is that collecting urine samples from young pre-continent children is difficult. Current collection methods all have limitations. Non-invasive methods (urine bag, waiting for clean catch) are time-consuming and often unsuccessful. Invasive methods (catheterisation, needle aspiration) are painful and distressing procedures that require specialist expertise. Choice of collection method must balance time, resources, invasiveness, and reliability.

There is a lack of research indicating the ideal collection method. International guidelines have conflicting recommendations. The literature shows clinicians have different preferences, [134] often don't adhere to local guidelines, [125] and frequently prescribe untargeted antibiotics without obtaining a urine sample at all. [124] Inadequate sample collection provokes a cascade of further problems: missed diagnosis, misdiagnosis, untargeted antibiotics and unnecessary

investigations. This is detrimental to patient care and wastes healthcare resources. The cost-effectiveness of collection methods was previously unknown.

The solution would be a quick and simple way to collect the necessary samples. Improved non-invasive urine sample collection is highlighted in the literature as a research priority. [15]

9.2 REVIEW OF RESEARCH AIMS AND METHODS

This PhD research had the overall objective to improve non-invasive urine sample collection for young pre-continent children.

Specific aims of the research were to discover and evaluate:

1. A quick, simple and effective non-invasive collection method
2. The costs and cost-effectiveness of current and new collection methods
3. Which collection methods are practical in the primary care setting
4. Knowledge translation of findings into practice, policy and guidelines

These aims were examined with the following research methodologies:

1. Pilot study and RCT of the novel Quick-Wee voiding stimulation method
2. Economic evaluation of existing and new collection methods
3. Exploratory qualitative study in Australian general practice
4. Clinical guideline update and development of consumer resources

9.3 ACHIEVEMENT OF AIMS & INTERPRETATION OF RESULTS

9.3.1 A simple and effective non-invasive collection method

The doctoral candidate conceptualised the novel Quick-Wee voiding stimulation method, using cold wet gauze to gently rub the suprapubic region. This triggers cutaneous voiding reflexes for faster and more successful urine

sample collection from young pre-continent children. The Quick-Wee pilot study (n=40) demonstrated the feasibility of this new method, and 30% of children voided within 5 minutes with the intervention. Parental and clinician satisfaction was high, with no adverse events.

The Quick-Wee RCT (n=354) provided definitive evidence that the method is effective for infants aged 1-12 months. The rate of voiding within 5 minutes was significantly higher with Quick-Wee compared to standard clean catch collection (31% vs 12% favouring Quick-Wee, P<0.001). Parental and clinician satisfaction was also higher for Quick-Wee than for standard clean catch (median 2 vs 3 on a 5 point Likert scale) with no adverse events, and contamination was lower but this result was not statistically significant. The number needed to treat was 4.7 to successfully collect one additional sample within 5 minutes using Quick-Wee compared to standard clean catch. The Quick-Wee RCT is the largest ever trial of a voiding stimulation method, and the only randomised trial to include older infants.

The existing literature shows that a combined bladder tapping and lumbar massage method, performed with the child held suspended under the arms, has a high success rate in a neonatal intensive care setting. [140 234] Several studies evaluating this method were published by other authors during the doctoral candidature. However there are no randomised studies outside the neonatal age range, and many of these studies included mandatory feeding before collection attempts and excluded participants with poor hydration, introducing a high risk of selection bias. [243] The non-randomised studies in the ED setting found lower success and difficulties with older infants, and 3 operators are required. [236 239 240] Therefore current evidence suggests the bladder-lumbar method is effective for neonates but less feasible for older infants in busy clinical settings like the ED.

A major strength of the Quick-Wee method is that it is a simple, single operator technique that can be easily utilised in any clinical setting. No additional resources are required beyond a piece of wet gauze. Evidence for efficacy and acceptability comes from a large, robust, randomised trial. While

collection success is significantly improved with this simple intervention, success is not universal, and sample contamination remains higher compared to invasive collection methods.

The findings of this research are relevant to a broad range of clinicians in primary care, paediatrics and emergency medicine, including in resource-limited settings.

Quick-Wee is a simple and effective voiding stimulation method that significantly increases the 5 minute success rate of non-invasive urine sample collection in young infants. The Quick-Wee method is also more acceptable to parents and clinicians than standard clean catch collection.

9.3.2 Cost-effectiveness of current and new collection methods

The doctoral candidate designed and conducted an economic evaluation, measuring and modelling the costs and cost-effectiveness of urine sample for young pre-continent children. This included the commonly used urine bag, clean catch, catheterisation and SPA methods, as well as the new Quick-Wee method, adopting a hospital costs perspective.

Overall, catheterisation was the favoured method from a hospital costs perspective to collect a definitive sample (£49.39 / $102.60). Quick-Wee was the favoured non-invasive collection method (£52.25, $108.53). Urine bags were the most expensive method (£112.28, $233.23). Time spent occupying a hospital bed was the most significant determinant of cost. Urine sample collection accounted for 20-50% of the total costs of ED UTI presentations, depending on collection method.

This is the first study to directly measure and compare the actual costs and cost-effectiveness of urine sample collection by collection method. A probabilistic model considered all of the pragmatic considerations required to reach a clinically definitive decision to diagnose or exclude UTI. This included

the initial collection attempt, actually obtaining a sample, dipstick screening and subsequent culture results. Model inputs were comprehensively informed by the published literature, prospective process mapping (n=40) and a survey of expert clinicians (n=20).

The model assumed that if initial collection attempts were unsuccessful, the clinician would proceed directly to catheterisation to collect a sample. This may not reflect practice in all clinical settings but was a necessary assumption to complete the model. Results are generalisable to EDs and hospitals within healthcare systems similar to Australia, but are not directly generalisable to primary care settings.

This is the first cost-effectiveness analysis of its kind, filling a significant evidence gap. Results show the Quick-Wee method is cost-effective, saving up to $125 per child compared to other non-invasive methods.

9.3.3 Practical methods for the primary care setting

This qualitative study explored the barriers and enablers to collecting urine samples from young children in primary care, with 25 semi-structured interviews with Australian GPs and practice nurses.

Non-invasive methods (urine bags, clean catch) were strongly favoured by primary care clinicians, although clean catch was considered to be time-consuming and urine bags were known to be frequently contaminated. Parents often performed the actual collection either in the clinic or at home. Invasive methods (catheterisation, SPA) were rarely used except by rural and remote clinicians, and these procedures were considered more suited to acutely unwell children in hospital settings. Five main themes emerged including clinician knowledge and experience, patient characteristics, parental understanding and motivation, the collection process itself, and the probable outcome of the collection method. Key barriers identified included the time

and space constraints in clinics, and key enablers included parental motivation, education handouts and voiding stimulation methods.

This is the first study to explore in depth and detail the barriers and enablers to urine sample collection from young children in the primary care setting. Clinicians (doctors and nurses) from a diverse range of primary care clinical settings were interviewed. Findings provide important insights into how clinicians choose and actually perform urine sample collection within the resource constraints of primary care, including time and space availability. Results are consistent with the existing literature and build on previous survey data and findings from other specialties. A limitation of this study is that while sample collection was often performed by parents, parents and carers were not interviewed directly to establish their views. Findings are informative for practice and policy in countries with primary health care systems similar to Australia.

Time, space and resource availability strongly influences how clinicians collect urine samples from young children in primary care settings. These findings can inform guidelines, policy, education and future research, and guide knowledge translation and implementation of best practice.

9.3.4 Knowledge translation of findings into practice

Knowledge translation activities were undertaken to facilitate use of the new Quick-Wee method and inclusion into clinical guideline recommendations.

Direct outputs arising from this doctoral work included the 5 research publications included in this thesis, 4 clinical review publications, and 12 conference presentations. The doctoral candidate was also the lead author updating local and statewide clinical practice guidelines, which now recommend use of the Quick-Wee voiding stimulation method. Two consumer education handouts for parents and carers were also updated to complement

the guideline, showing how to perform the Quick-Wee method using a simple "clean, rub, catch" 3-step process.

The doctoral research findings have been translated into policies and guidelines within a short timeframe, with the Quick-Wee method now recommended in 14 clinical practice guidelines in Australia, Canada, Italy, Finland, the Netherlands, the US and the UK. Further translation may continue to occur as other guidelines are updated in the future.

Knowledge generated from this doctoral research has been successfully translated into clinical practice guidelines in Australia and internationally.

9.4 OVERALL STRENGTHS OF THE RESEARCH

The novel Quick-Wee voiding stimulation method and this doctoral research series has a number of strengths overall, including:

- simplicity
- effectiveness
- cost-effectiveness
- acceptability
- the robust methods used to generate this new knowledge

9.4.1 Simplicity

"We believe these simple yet effective methods will save time and aggravation for clinicians who require urine collection in patients where invasive testing is unavailable or not indicated."

Jaffer & Muselius (2017) [312]

The Quick-Wee method was designed to be simple and require only a single operator. It is quick to perform, and easy to incorporate into routine clinical

practice. No specialist equipment or expertise is required, so the method can be easily performed across primary care, emergency and hospital settings, and can be implemented in resource-limited settings.

9.4.2 Effectiveness

"Just under a third (31%) of infants passed urine within five minutes when the Quick-Wee method was used, compared with 12% using the standard clean catch method, a clinically relevant and statistically significant difference."

Kilonback (2017) [123]

The Quick-Wee method increases the speed and success of non-invasive urine sample collection, improving the quality and timeliness of patient care during evaluation of potential UTI, and improving health service efficiency. Improved non-invasive collection may spare some children from invasive and painful catheter and needle procedures.

Improved non-invasive sample collection has additional downstream benefits. Accurate and timely UTI diagnosis leads to targeted and timely treatment. Accurate evaluation reduces UTI misdiagnosis and untargeted antibiotic therapy due to sample collection difficulties, and may reduce unnecessary imaging and follow-up from false-positive culture results. Timely treatment may help to reduce patient complications such as pyelonephritis, sepsis and renal scarring.

9.4.3 Acceptability

"The innovative Quick-Wee method requires minimal resources with good acceptance by both parents and clinicians."

Tran (2017) *313*

The Quick-Wee method is gentle for children, with higher parent and carer satisfaction than standard clean catch collection. Parental acceptability is important, as parents are often directly responsible for non-invasive collection attempts, both in clinical settings and at home.

The method is also practical for nurses and doctors, with higher clinician satisfaction than standard clean catch collection. Primary care clinicians identified the method as an enabling strategy for successful sample collection. Clinician acceptability is important, as clinicians have their own preferences for collection methods and do not always follow guideline recommendations.

9.4.4 Cost-effectiveness

"In constrained environments, where resources are scarce, healthcare providers often craft unexpected solutions to provide adequate healthcare to patients. These inexpensive but effective frugal innovations may be imperfect, but they have the power to improve people's lives by ensuring that health is within everyone's reach."

Tran & Ravaud (2016) [51]

Catheterisation was the most cost-effective sample collection method for young pre-continent children from a hospital costs perspective. For paediatric UTI guidelines that recommend the catheter method as first line, such as the American and Canadian guidelines, this finding complements the existing clinical evidence supporting this collection method.

The Quick-Wee method was the most cost-effective non-invasive collection strategy for young pre-continent children. The Quick-Wee method saves time, and in hospitals time is money. Costs for Quick-Wee were only slightly higher than for invasive methods, and invasive methods are not practical in all clinical settings. Many guidelines recommend non-invasive collection methods as first line, including Australian and UK guidelines. Practice change towards invasive catheter and SPA methods is unlikely to be driven by evidence of

cost-effectiveness alone. However adopting the Quick-Wee method into policy and practice where non-invasive collection is recommended has the potential for significant aggregate hospital cost savings.

9.4.5 Rigour of the research and significance of findings

"The bladder stimulation techniques evaluated appear to offer some hope in the long-standing challenge of obtaining urine samples for clinical evaluation in non-toilet trained children. … The highest quality evidence currently is provided by the study by Kaufman et al ('Quick-Wee' method)…"

Chandy et al (2020) [243]

Research methods for all parts of the doctoral research series were rigorous, and followed recommended international reporting guidelines. Clinical evidence is provided from an initial pilot study and subsequent randomised trial. This is complemented by economic evidence from a detailed health economic evaluation. Qualitative data has provided unique insights into clinical practice in primary care, informing translation, future research and guidelines.

This research therefore has demonstrated strong evidence for a triple dividend of effective, cost-effective and acceptable care.

9.5 OVERALL LIMITATIONS OF THE RESEARCH

All research has limitations, which for the Quick-Wee method and this research series includes the partial success rate for sample collection, hospital research setting, and unchanged contamination rate.

9.5.1 Success rate

The Quick-Wee method was nearly three times more effective than standard clean catch practice to achieve voiding and urine sample collection within 5 minutes. There is much to gain and little to lose from trying this method when non-invasive collection is appropriate.

However many infants did not void within 5 minutes with Quick-Wee, and therefore this new method is not a panacea for all the challenges of urine sample collection in this age group. Existing collection methods are still required in clinical practice.

9.5.2 Research setting

The two clinical trials in this research series were conducted in a tertiary paediatric hospital ED. The ED setting facilitated optimal participant recruitment, but ideally further trials should be conducted to replicate and validate findings in other settings, particularly in primary care.

The economic evaluation in this research series adopted a hospital costs perspective, and was informed by hospital data. An evaluation adopting a primary care perspective, informed by reliable primary care data, would help inform practice and policy specific to the primary care setting.

9.5.3 Contamination

Sample contamination for non-invasive methods remains a prominent clinical concern. Bag urine collection has a contamination and false positive rate of around 50%, a level unacceptable to many clinicians. Clean catch has a much lower rate of contamination of around 25%, though this is still much higher than invasive methods. Lowering the contamination rates of non-invasive collection methods would substantially increase their clinical utility.

Contamination was not a primary outcome measure for the clinical trials in this research series. The randomised trial was powered for collection success and not all infants voided within 5 minutes, so the trial was underpowered to identify a significant difference in contamination between Quick-Wee and standard clean catch methods if one exists.

9.6 IMPLICATIONS FOR PRACTICE AND POLICY

The Quick-Wee method is more effective, more cost-effective, and more acceptable than standard clean catch collection. It is gentle for children and simple for clinicians. Contamination is lower than for bag urine collection.

Therefore, there is strong evidence to adopt the use of voiding stimulation methods in general, and the Quick-Wee method specifically, as the first-line strategy for non-invasive urine sample collection in young pre-continent children. Change in practice and policy has begun, with the research findings already adopted into some guidelines locally and internationally, although further efforts are required to continue knowledge translation.

Contamination remains higher than for invasive collection methods and therefore for some high acuity clinical indications, such as the septic neonate, the Quick-Wee method will not be the preferred collection method.

9.7 FUTURE DIRECTIONS

Two projects have been designed by the doctoral candidate directly arising from this PhD research, who is supervising paediatric specialty trainees and medical students undertaking parts of each project.

9.7.1 Defining the paediatric UTI antimicrobiogram

Globally antimicrobial resistance is increasing, but local data on UTI antimicrobial resistance is limited.

This study will be a single centre retrospective observational study with a 10 year analysis of all paediatric urine samples defining rates of antimicrobial resistance. This will be the largest ever Australian cohort study quantifying paediatric UTI antimicrobial resistance, which will directly inform Australian guideline recommendations for empiric antibiotic therapy. This research will be conducted with in-kind support from local clinicians and researchers.

Sample contamination rates will also be analysed to allow for sample size estimation for the RCT described below in section 9.7.2.

9.7.2 Reducing sample contamination

Avoiding contamination during non-invasive urine sample collection remains a major challenge. The perigenital skin is colonised with bacteria, and urine flushes against the skin when children void, contaminating the sample with incidental skin flora. Few clinical guidelines have specific recommendations for pre-collection skin cleaning, and there is no evidence to support specific cleaning strategies in young pre-continent children.

This 4-part postdoctoral research series will investigate whether a simple skin cleaning intervention using a dilute antiseptic solution can reduce non-invasive sample contamination.

1. SURVEY

Survey of 200 clinicians to define current local skin cleaning practices.

2. PILOT STUDY

Pilot feasibility study of the intervention for 100 pre-continent children who require non-invasive urine sample collection.

3. RCT

Prospective single centre RCT of intervention compared to standard practice.

4. HEALTH ECONOMICS

Preliminary economic evaluation to demonstrate the potential cost savings of the intervention.

The overall aim of this planned research series is to provide foundation data to inform a larger multicentre randomised trial. Parts 1 and 2 of this research have been supported by an Early Career Research Grant from the Western Health Foundation, awarded to the doctoral candidate in 2020.

Chapter 10 CONCLUSIONS

"A simple suprapubic stimulation technique increased the number of infants who provided a clean-catch voided urine sample within 5 minutes - a clinically relevant and satisfying outcome."

Morris & Mounsey (2018) [314]

Urinary tract infections (UTIs) are very common in young children, but hard to diagnose, and easily missed. Diagnosis is important: if untreated UTI can cause sepsis and permanent kidney scarring. A urine sample is required to check for UTI, so guidelines recommend all young children with unexplained fever must have a urine sample tested. This is required for many children in primary care and hospital settings.

The problem is that collecting urine samples from young children is extremely difficult. Existing collection methods all have limitations. Standard care in Australia of waiting for a clean catch is time-consuming and often unsuccessful. Urine pads and bags have unacceptably high contamination. Catheter and needle procedures are painful and distressing, and require expertise and equipment to perform. For one of the most common infections of early childhood, we have been equipped with either inadequate or invasive methods of evaluation.

Suboptimal practice compromises patient care and wastes healthcare resources. The solution would be a quick and simple way to collect the necessary samples. The concept for a new voiding stimulation method evolved into this PhD research series.

The novel Quick-Wee method involves gently rubbing the lower abdomen with wet gauze, triggering bladder reflexes and urine voiding, so samples can be collected quickly. A large randomised trial showed Quick-Wee is three times more effective than standard care, and is preferred by parents and clinicians. An economic evaluation found Quick-Wee is substantially cheaper than other

non-invasive methods. Qualitative research identified barriers to best practice in primary care, and informed implementation, knowledge translation and future research.

The new Quick-Wee voiding stimulation method is more effective, more cost-effective, and more acceptable than standard care. It is gentle for children and simple for clinicians. This research has addressed key evidence gaps, contributing new knowledge to optimise investigation of UTI in young children. Findings have been incorporated into policies and guidelines internationally.

Chapter 11 APPENDICES

11.1 PUBLICATIONS NOT INCLUDED IN THESIS CHAPTERS

11.1.1 Paper 1

Open access Review

BMJ Paediatrics Open

Urinary tract infections in children: an overview of diagnosis and management

Jonathan Kaufman,[1,2,3] Meredith Temple-Smith,[3] Lena Sanci[3]

To cite: Kaufman J, Temple-Smith M, Sanci L. Urinary tract infections in children: an overview of diagnosis and management. *BMJ Paediatrics Open* 2019;**3**:e000487. doi:10.1136/bmjpo-2019-000487

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ABSTRACT

Urinary tract infections (UTIs) are a common and potentially serious bacterial infection of childhood. History and examination findings can be non-specific, so a urine sample is required to diagnose UTI. Sample collection in young precontinent children can be challenging. Bedside dipstick tests are useful for screening, but urine culture is required for diagnostic confirmation. Antibiotic therapy must be guided by local guidelines due to increasing antibiotic resistance. Duration of therapy and indications for imaging remain controversial topics and guidelines lack consensus. This article presents an overview of paediatric UTI diagnosis and management, with highlights of recent advances and evidence updates.

BACKGROUND

Prevalence and epidemiology

Urinary tract infection (UTI) is one of the most common bacterial infections of childhood. Among febrile infants, unwell children in general practice and older children with urinary symptoms, 6%–8% will have a UTI.[1 2] Prevalence varies with age, peaking in young infants, toddlers and older adolescents. UTI is more common in female and uncircumcised male infants,[1] understandable given bacterial skin flora concentration under the nappy in infancy, shorter female urethral distance and foreskin surface area in uncircumcised males. During toddler years, toilet training can lead to volitional holding and bladder stasis, promoting UTIs.[3] Prevalence peaks again in adolescent females when sexual activity disrupts bacteria near the urethral orifice.[1]

Conditions that impair urinary flow increase susceptibility to UTI. Voiding flushes bacteria out of the urinary system.[3] Impaired urine flow leads to urinary stasis, giving bacteria an increased reservoir and more time to establish infection. Causes of disordered voiding can be structural (urogenital anomalies) or functional (neurogenic bladder, constipation and behavioural withholding). Altered immune function can increase the risk of uncommon viral and fungal causes of UTI.

Over 30% of children with UTI will have recurrent UTI.[4] Common risk factors for recurrence include vesicoureteric reflux (VUR) and bladder–bowel dysfunction.[4] Older non-continent children (eg, developmental delay) also have more recurrent UTIs.

Being such a common infection, UTI contributes a significant economic burden to the healthcare system. Use of evidence-based management has the potential for significant cost savings.[5]

Aetiology

Most paediatric UTIs are caused by Gram negative coliform bacteria arising from faecal flora colonising the perineum, which enter and ascend the urinary tract.[3] *Escherichia coli* (*E.coli*) is the most common uropathogen, responsible for approximately 80% of paediatric UTIs.[6] Uropathogenic *E.coli* strains possess specific properties, such as fimbriae to attach to the uroepithelial cell surface, to allow them to overcome host defences (figure 1).[3] Other common uropathogens include *Klebsiella*, *Proteus*, *Enterobacter* and *Enterococcus* species.[6 7]

Upper versus lower tract UTI

UTI can be categorised anatomically into upper tract and lower tract infection.[8] Upper tract UTI involves infection and inflammation in the kidneys (pyelonephritis) and ureters (figure 2). This typically leads to abdominal pain and loin tenderness, with systemic features such as fever, anorexia, vomiting, lethargy and malaise. Lower tract UTI involves infection within the bladder (cystitis) and urethra, with localised symptoms such as lower abdominal or suprapubic pain, dysuria, urinary frequency and urgency. Older children may present with signs and symptoms suggesting the site of infection. In younger patients, these classical signs are often absent, and differentiating between upper and lower UTI is less obvious.

Morbidity

Acute UTI encompasses the full spectrum of severity from mild dysuria in an otherwise well child to life-threatening urosepsis. While serious infections are less common, they can and do occur, particularly in neonates.[9] Since

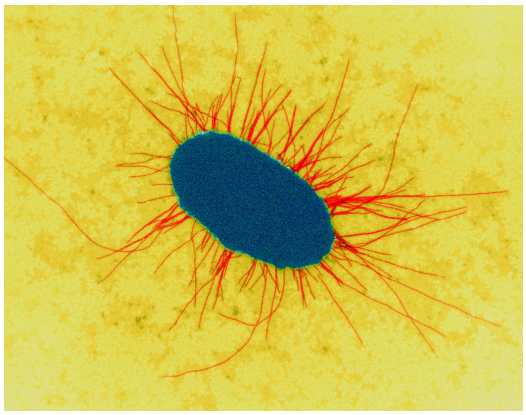


Figure 1 *Escherichia coli* with fimbriae. Image courtesy of Dennis Kunkel Microscopy, Science Photo Library.

routine immunisation for *Haemophilus influenzae* type B and *Streptococcus pneumoniae*, UTI has become a more common cause of occult and serious bacterial infection in infants.[8]

Short-term morbidity can arise from infection within the renal system. This includes systemic features including poor oral intake and dehydration, and uncommon local complications including perinephric abscess formation. Short-term morbidity also arises from haematogenous uropathogen spread. Bactaraemic UTI has been best studied in infants, as this population is most likely to have blood cultures collected during febrile illnesses. Approximately 5% of infants <12 months with UTI have bacteraemia identified,[10] depending on study setting.

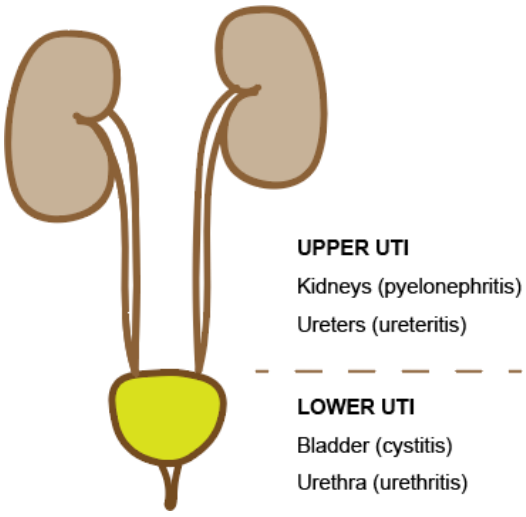


Figure 2 Urogenital system: upper versus lower tract UTI. Image courtesy of Dr Jonathan Kaufman. UTI, urinary tract infection.

Bacteraemia can then lead to urosepsis. Meningitis can also occur with haematogenous spread to the cerebrospinal fluid (CSF). The risk of coexisting meningitis and UTI is 1% in the neonatal period,[11] suggesting a low threshold to perform lumbar puncture in this age group. Beyond 1 month, the risk is smaller.[11] Typical empirical UTI antibiotics have poor CSF penetration and inadequate duration to treat bacterial meningitis.

Long-term morbidity follows renal injury and scarring from upper tract UTI. Around 15% of children with first UTI who have follow-up scanning will have evidence of renal scarring.[12] This scarring would be clinically important if it led to renal dysfunction, hypertension and chronic kidney disease (CKD). Historical thinking suggested these sequalae were common, leading to aggressive imaging guidelines to identify children at risk of CKD. Recent data suggest the risks are much lower. A 2011 systematic review of 1576 cases found no cases where childhood UTI was the main cause of subsequent CKD.[13] Of a further 366 local CKD patients in the same study, 13 (3%) had a history of UTI in childhood but all had renal abnormalities evident on renal ultrasound, and recurrent UTI was possibly the cause of CKD in only one case (0.3%).[13] Therefore, in the absence of structural renal anomalies or recurrent UTI, the risk of CKD appears minimal. Debate about the significance of post-UTI renal scarring continues.

DIAGNOSIS

Clinical features of paediatric UTI are remarkably non-specific, especially in younger children. Diagnosis can be challenging but is important to consider, especially for infants with fever without focus.

History

Younger preverbal children cannot report symptoms such as dysuria or abdominal pain. Parents often notice non-specific signs, such as lethargy, irritability, poor feeding and vomiting. These overlap with many common and benign viral infections, as well as serious bacterial infections. Fever is often present, may be the only feature present or the child may be afebrile. Malodorous or discoloured urine may be obscured in nappy-wearing children. Older children may report localising symptoms such as dysuria or flank pain.

Examination

Children with UTI may appear very well or very unwell. Fever, abdominal tenderness and dehydration may be identified. Localising signs are more likely in older children. As clinical diagnosis is unreliable, a urine sample is required for further evaluation.

Urine sample collection: continent children

Continent children can void on request to provide a midstream urine (MSU) sample into a sterile collection jar. The first voided urine flushes skin flora away from

the urethral orifice, before sample collection from the middle of the urinary stream. Cleaning with soap and water before MSU further reduces contamination.[14]

Urine sample collection: precontinent children

Young children in Western society generally do not achieve urinary continence until 2–3 years old, so other collection methods are required for precontinent children. Non-invasive methods involve waiting for spontaneous urine voiding, then opportunistic collection with a nappy pad, bag, or 'clean catch' of the urine stream. These methods seem convenient and practical. However, pads and bags have high rates of contamination up to 50%–60%,[2 15] understandable given their close contact with skin under the nappy area. Pad and bag samples can be useful for dipstick screening but are unreliable for culture. Cotton wool ball collection is specifically discouraged.[16] Clean catch has the lowest contamination of all non-invasive methods at around 25%,[17] but attempts can be time-consuming or unsuccessful. Simple voiding stimulation methods such as the Quick-Wee technique can increase the speed and success of clean catch.[18 19]

Invasive methods extract urine directly from the bladder by urethral catheterisation or suprapubic needle aspiration (SPA). These methods are effective but require expertise and equipment to perform and are painful and distressing for the child. Contamination from catheter and SPA is low, at 10% and 1% respectively,[17] so these methods are more reliable for culture and diagnosis.

The optimal collection method remains controversial (table 1). Each method has advantages and limitations, and guidelines have different recommendations.[20] In the UK, where general practitioners provide primary care, guidelines recommend clean catch or other non-invasive methods if clean catch is not possible, and catheter or SPA only if non-invasive methods are not possible or practical.[16] In the USA, where paediatricians often provide primary care, guidelines recommend the opposite, that catheter or SPA is required to confirm UTI, though convenient methods such as urine bags can be used for screening.[21] Most international guidelines recommend catheter or SPA as the gold standard, include clean catch as an acceptable collection method, and specifically discourage the use of bag samples for culture.[22–24] A two-step process using initial bag screening and catheter confirmation of positive screens can reduce the rate of invasive procedures.[25]

Who needs evaluation for UTI

Clinical diagnosis of UTI is unreliable, so many children with fever or symptoms of UTI need a urine sample to exclude or make the diagnosis. Urine samples should be collected before starting antibiotics, but therapy should not be delayed in the septic child.

Children with localising signs or suspected UTI need a urine sample to confirm the diagnosis.[16]

Children with fever without focus, particularly neonates and infants, need a urine sample to evaluate potential

Table 1 Urine collection methods for precontinent children

	Non-invasive methods			Invasive methods	
	Nappy pad	**Urine bag**	**Clean catch**	**Catheter**	**SPA**
Procedure	Pad placed inside nappy.	Bag affixed over genitalia.	Wait until child voids spontaneously, catch sample opportunistically.	Catheter inserted into bladder via urethra, removed once urine sample obtained.	Needle inserted into bladder through skin of lower abdomen above pubic symphisis.
Advantages	Convenient. Useful for dipstick screening.	Convenient. Useful for dipstick screening.	Least contamination of non-invasive methods. Voiding stimulation methods can increase success.	Low contamination. High success rate.	Ultra-low contamination. Ultrasound to confirm adequate bladder filling can increase success.
Limitations	High contamination. Unreliable for culture.	High contamination. Unreliable for culture.	Moderate contamination. Can be time-consuming.	Invasive and painful. Requires equipment and expertise.	Invasive and painful. Requires equipment and expertise.
Contamination rate	>60%[2]	≈50%[15 17]	25%[17]	10%[17]	1%[17]
Cost per definitive sample in an emergency department setting	–	£112.28[47]	£64.82 standard clean catch or £52.25 with 5 min voiding stimulation[47]	£49.39[47]	£51.84[47]

SPA, suprapubic needle aspiration.

UTI. Outside early infancy and if the child is not unwell, it may be reasonable to wait 24 hours for collection to see if an alternative focus emerges.[16]

Children with an alternative focus of illness generally do not need a urine sample.[16] Exceptions are septic infants, children with predisposing conditions (eg, renal anomalies), children at risk of complications (eg, single kidney) and febrile illness not following the expected clinical course.

Screening – dipstick and microscopy

Urine dipsticks are a quick, inexpensive bedside screening tool. Chemical reagent strips change colour in the presence of leucocyte esterase (an enzyme present in leucocytes) and nitrites, which may arise from UTI.[26] Leucocytes generally appear in the urine in response to UTI. However, sterile pyuria can occur with other infections. *Enterococcus*, *Klebsiella* and *Pseudomonas* species are also less likely to produce pyuria than *E.coli* in children with symptomatic UTI.[27] Most uropathogens convert dietary nitrates into urinary nitrites. However, not all do, including *Enterococcus* and *Klebsiella* species.[26] Dipsticks are also less reliable in young infants, where frequent voiding flushes substrates out of the bladder.[26]

Neither leucocytes or nitrites are fully sensitive or specific for UTI, but they are a useful screening test, particularly when used in combination. If UTI is thought unlikely, dipsticks have a good negative predictive value to exclude the diagnosis.[28] In the presence of suggestive symptoms and either leucocytes or nitrites, empirical antibiotics while awaiting culture is indicated.[16]

Urine microscopy also identifies leucocytes and bacteria, augmenting dipstick screening.

Diagnosis: culture

Laboratory culture is the gold standard for UTI diagnosis. Urine is sterile; therefore, the presence of bacteria in sufficient quantity, with concurrent evidence of active infection, suggests UTI. Urine is added to a growth medium, from which bacteria and antibiotic sensitivities are identified. Culture takes around 24 hours, then the presumptive diagnosis can be reviewed. All major UTI guidelines recommend culture is required for UTI diagnosis.[16 21]

How many bacteria are needed to diagnose UTI in children? Thresholds vary between guidelines and collection methods.[24 29] The commonly quoted threshold of 100 000 CFU/mL of a single organism is based on a seminal study in adult women by Kass[30] from 1956. Does this threshold apply in children? American guidelines suggest a 50 000 CFU/mL threshold with concurrent pyuria for SPA and catheter specimens.[21] More recent evidence suggests an even lower 10 000 CFU/mL threshold would slightly increase sensitivity without reducing diagnostic specificity.[29] Many guidelines suggest that any growth on SPA is abnormal,[24] as SPA has negligible contamination.

Asymptomatic bacteriuria (ASB) is the presence of bacteria in the urine without active infection. ASB prevalence is estimated at 1.4%–1.9% in childhood.[31 32] Bacterial growth without evidence of active infection (eg, pyuria) does not suggest UTI.

In reality, these diagnostic thresholds are not binary.[16] Low colony counts on culture may represent early infection, contamination or ASB. Pyuria may occasionally be absent in early infection or immunocompromise. Screening and culture results must always be considered in the clinical context.

Contamination

Contamination muddies the waters when evaluating UTI. Assuming a single uropathogen causes UTI, multiple organisms suggests sample contamination. Incidental flora colonise the perigenital skin and can get flushed into the urine sample on voiding. Missed diagnosis can occur if a true uropathogen is concealed in the mix or misdiagnosis if a single contaminant dominates the culture. Contamination can be minimised by cleaning the perigenital skin before sample collection[14] and avoiding touching inside the specimen jar or holding the jar against the child's skin.

What is on the horizon?

Current tests for UTI lack absolute sensitivity or specificity. Urinary biomarkers such as interleukin 6 and neutrophil gelatinase-associated lipocalin have been proposed to differentiate between active infection and ASB. Real-time PCR has been proposed to identify common uropathogens such as *E.coli*.[28] Further research is required to understand the clinical utility of these emerging tests.

INITIAL MANAGEMENT

General

Children with UTI require targeted antibiotics and supportive care. Most children with UTI can be managed at home with oral fluids and antibiotics. A small percentage will require admission for intravenous therapy, including very young and very unwell children, children with significant renal tract anomalies and children not responding to oral therapy.

Antibiotic therapy

Choice of empiric antibiotics must be guided by local guidelines, as local antimicrobial sensitivities vary significantly (table 2). The suitability of the initial agent should be reviewed once culture results are available.

Oral antibiotics are effective for the overwhelming majority of paediatric UTI. Previous Cochrane reviews suggest that short 2–4 days courses are as effective as longer 7–14 days for uncomplicated cystitis,[33] while single dose therapy is less effective.[34] American guidelines recommend treatment durations of 7–14 days for both cystitis and pyelonephritis,[21] Canadian guidelines recommend 7–10 days,[35] while National Institute for Health and

Table 2 Recent evidence, controversies and emerging evidence

RECENT EVIDENCE	
Urine bag collection	High contamination rates ≈50%.[15 17] Least cost-effective collection method.[47] Useful for dipstick screening but unreliable for culture.
Voiding stimulation methods	Improves the speed, success and cost-effectiveness of clean catch urine collection in precontinent children[16 18]
Antibiotic prophylaxis	Not recommended after first or second UTI in otherwise healthy children. Modest effect on recurrence, does not reduce scarring and increases antibiotic resistance.[44–46]
CONTROVERSIES	
What colony counts on culture represent true UTI?	Historical: 100 000 CFU/mL.[30] NICE: no specific recommendation.[16] AAP: 50 000 CFU/mL from catheter/SPA sample with pyuria.[21] Proposed: 10 000 CFU/mL with symptoms/pyuria.[29]
Duration of antibiotic therapy?	Short-course therapy for lower tract UTI (cystitis) may be as effective as longer courses.[33] NICE: 7–10 days for pyelonephritis and 3 days for children >3 months with cystitis[16] AAP: 7–14 days for all UTI.[2]
Choice of antibiotic agent?	Must be guided by local guidelines and sensitivity patterns, as susceptibility can vary significantly between regions.[21]
Does uncomplicated UTI predispose to risk of chronic kidney disease?	Children with structurally normal kidneys appear not at significant risk of long term renal morbidity.[9 13]
Imaging tests following UTI: who, what and when to image?	Historical: aggressive imaging to identify VUR and scarring. NICE: age and risk based approach.[16] AAP: ultrasound for all children <2 years old with febrile UTI, VCUG if ultrasound is abnormal.[21]
EMERGING EVIDENCE	
Antibiotic resistance	Increasing globally, highest in resource-limited settings.[6 37] Increases healthcare costs.[38]
Urinary biomarkers to differentiate between UTI and asymptomatic bacteriuria	For example, interleukin-6, neutrophil gelatinase-associated lipocalin: further research needed to establish clinical utility.[28]
Point-of-care PCR to identify presence of uropathogens	Can identify common uropathogens but only specified targets so may miss uncommon bacterial species. Cannot differentiate between contamination, asymptomatic bacteriuria and infection.[9]

National Institute for Health and Care Excellence (NICE) UK Clinical Guideline 54: UTI in under 16s: diagnosis and management 2017.
American Association of Paediatrics Clinical Practice Guideline: the diagnosis and management of the initial UTI in febrile infants and young children 2–24 months of age 2016.
PCR, Polymerase Chain Reaction; SPA, suprapubic needle aspiration; UTI, urinary tract infection; VCUG, Voiding Cystourethrogram; VUR, vesicoureteric reflux.

Clinical Excellence (NICE) guidelines suggests 7–10 days for pyelonephritis and a shorter 3 day course for children >3 months with cystitis.[16] Spanish guidelines mirror NICE recommendations though single-dose therapy is recommended for children aged >6 years with uncomplicated cystitis.[36]

Younger and sicker children may require initial intravenous therapy. Many guidelines and centres recommend admission, intravenous antibiotics and consideration of septic work-up for infants <3 months.[16] Aim to switch to oral therapy after 48 hours if there is clinical improvement.

Antibiotic resistance

Antibiotic resistant UTI is becoming more common globally,[6 37] increases morbidity and doubles healthcare costs.[38] The usual mechanism is through acquisition of enhanced beta-lactamase enzyme properties. Some Gram negative uropathogens can inactivate beta-lactam ring antibiotics such as penicillin and early generation cephalosporins with inherent beta-lactamase enzymes. However, some have acquired further multidrug-resistant properties through evolution of these enzymes, including the ability to hydrolyse and inactivate extended spectrum cephalosporins and carbapenem antibiotics.[39] Such organisms are known as extended spectrum beta lactamase (ESBL) organisms. Prior antibiotic therapy and hospitalisation are risk factors for ESBL carriage, which then contributes to community carriage and transmission of resistance. Rates of resistant UTIs are particularly high in resource-limited settings,[37] where resistance to common oral antibiotics such as ampicillin and cotrimoxazole can be as high as 97%–100%.[40]

Table 3 Summary of imaging recommendations from selected international guidelines for young children with UTI

	Recommended imaging test(s)
National Institute for Health and Clinical Excellence (NICE) UK[16]	
Age 0–6 months	
Uncomplicated first UTI	Outpatient ultrasound.
Atypical UTI	Inpatient ultrasound, outpatient DMSA scan and VCUG.
Recurrent UTI	Inpatient ultrasound, outpatient DMSA scan and VCUG.
Age 6 months–3 years	
Uncomplicated first UTI	No imaging.
Atypical UTI	Inpatient ultrasound, outpatient DMSA scan.
Recurrent UTI	Outpatient ultrasound, outpatient DMSA scan.
Age >3 years	
Uncomplicated first UTI	No imaging.
Atypical UTI	Inpatient ultrasound.
Recurrent UTI	Outpatient ultrasound, outpatient DMSA scan.
American Academy of Pediatrics (AAP)[21]	
Age 0–24 months	
Any febrile UTI	Ultrasound.
Complex or atypical circumstances	VCUG.
Recurrent UTI	Further evaluation.
Canadian Paediatric Society (CPS)[35]	
Any febrile UTI aged <2 years	Ultrasound.
European Association of Urology/European Society for Paediatric Urology23	
Any febrile UTI	Ultrasound.
Suspicion of VUR and/or pyelonephritis	VCUG and/or DMSA scan.
Spanish Association of Paediatrics[36]	
UTI that requires admission, is recurrent or with suspected complications	Inpatient ultrasound.
First UTI if aged <6 months	Outpatient ultrasound.
Recurrent or atypical UTI	Outpatient ultrasound, and VCUG or contrast enhanced bladder ultrasound especially if aged <6 months, and DMSA scan especially if aged <3 years.

Uncomplicated UTI: responds well to appropriate treatment within 48 hours.
Atypical UTI: includes very unwell/sepsis, abnormal urine flow or renal function, non-*Escherichia coli* uropathogen.
Recurrent UTI: ≥3 episodes of cystitis or ≥2 episodes of UTI including at least one episode of pyelonephritis.
Inpatient ultrasound: during acute infection.
Outpatient ultrasound: within 6 weeks.
Outpatient DMSA scan: 4–6 months following UTI to differentiate acute infection from scarring.
NICE, CPS and AAP guidelines suggest consider VCUG if abnormal ultrasound, for example, dilation suggesting severe VUR, obstruction and scarring.
DMSA, dimercaptosuccinic acid; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUR, vesicoureteric reflux.

IMAGING

Historically, guidelines recommended aggressive imaging follow-up to identify renal scarring and complications from UTI. It is now known that the most children at risk of complications have structural abnormalities identifiable on ultrasound or recurrent UTI. Therefore, many recent guidelines suggest less or no imaging after first uncomplicated UTI for older children and less aggressive imaging after recurrent UTI (table 3).[24]

Ultrasound

Ultrasound is non-invasive, relatively inexpensive and an appropriate first-line investigation when imaging is indicated. Ultrasound can detect anatomical abnormalities and hydronephrosis or hydroureter suggesting obstruction or VUR. American and Canadian guidelines recommend ultrasound for all children aged <2 years with first UTI,[21 35] European Association of Urology guidelines recommend ultrasound for all children with first febrile UTI,[23] while NICE recommends ultrasound only for

infants<6 months with first UTI unless infection is atypical or not responding to treatment.[16] The NICE approach reflects the view that routine imaging after all first UTI is not cost-effective; however, imaging in younger children and other selected cases is more likely to detect findings of clinical significance.[41] Ultrasound cannot exclude all cases of VUR but should detect most higher grade and clinically significant cases.

Dimercaptosuccinic acid (DMSA) scan

DMSA scan is a nuclear isotope uptake scan. Reduced uptake in the kidney can reflect either acute dysfunction (pyelonephritis) or long term damage (scarring), depending on the timing of the test.[9] It is rarely required acutely but may help guide long-term management. DMSA may be indicated if UTI is atypical, recurrent or if initial ultrasound is significantly abnormal.

Voiding cystourethrogram (VCUG)

VCUG uses fluoroscopy (real-time X-ray) to identify the course of contrast inserted by bladder catheterisation. Bladder filling, emptying and ureteric reflux can be identified. While VCUG is the gold standard for identifying and quantifying VUR, the procedure has a radiation burden and is invasive.

Consensus for exactly who and how to image is lacking. Cost, invasiveness and radiation burden must be balanced against the likelihood of identifying an abnormality which may change management for the child. While most children with uncomplicated UTI outside infancy do not require any imaging, some children are at risk of long-term morbidity after UTI. Therefore, targeted imaging and surveillance strategies for children with selected indications remains appropriate.

SPECIAL CASES

Reflux: a state of flux

Historical approaches assumed VUR could lead to significant long-term renal damage, therefore should be identified early. There is now increasing awareness that much of the renal disease based on reflux is congenital, with an appreciation of mild hydronephrosis and VUR as likely normal physiological states that resolve spontaneously.[9 13 21] Given that lower grade reflux is unlikely to cause clinically significant scarring, and mild scarring without other risk factors is unlikely to cause long-term renal dysfunction, aggressive identification of all VUR is unwarranted. Active management strategies should still be considered for higher grade VUR (figure 3).[12]

Anatomical abnormalities

Anatomical abnormalities of the renal system can predispose to UTI morbidity but are now often (but not always) detected on routine antenatal ultrasound screening in developed settings. Significant abnormalities warrant appropriate follow-up.



Figure 3 Five-year-old girl with unilateral grade 4 vesicouretric reflux on voiding cystourethrogram. Image courtesy of Dr Aditya Shetty, Radiopaedia.org, rID: 2722.

Recurrent UTI: prophylaxis and prevention

There are few pragmatic strategies to reduce the risk of recurrent UTI in children. Circumcision reduces the risk of UTI in males, but involves surgery, with a number needed to treat of >100 to prevent one UTI.[42] There is insufficient evidence to support cranberry prophylaxis or probiotics.[43] Antibiotic prophylaxis has modest benefits, increases antibiotic resistance[44] and is not indicated after first or second UTI in otherwise healthy children.[45] For children with VUR, antibiotic prophylaxis reduces UTI recurrence but does not reduce scarring.[46] Simple hygiene such as wiping front to back in females can avoid introducing bacteria into the urethral orifice. Active management of toilet training and constipation is important to prevent functional bladder–bowel dysfunction.[4 21]

SUMMARY

UTI is a common bacterial infection of childhood. Clinical diagnosis is unreliable, and a urine sample is required for diagnosis, but collection is not straightforward in precontinent children. Dipstick leucocyte and nitrite screening can inform initial management while awaiting culture confirmation. Prompt management aims to prevent short-term morbidity such as urosepsis and long-term morbidity such as renal scarring. Recent evidence supports less aggressive imaging following uncomplicated UTI. Antibiotic resistance is an increasing challenge. International guidelines have conflicting recommendations regarding sample collection methods, antibiotic

duration and imaging indications. Targeted research is required to inform knowledge gaps and inform cost-effective care for paediatric UTI.

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Patient consent for publication Not required.

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How to… collect urine samples from young children

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ABSTRACT

Urine samples are commonly collected from young children to diagnose or exclude urinary tract infections, but collection from precontinent children is challenging. Each collection method has advantages and limitations. Non-invasive methods (urine pads, bags, clean catch) are convenient but can be time-consuming and are limited by sample contamination. Voiding stimulation methods (bladder-lumbar stimulation, Quick-Wee) can expedite clean catch collection. Invasive methods (catheter, suprapubic aspiration) can be more reliable, but require expertise to perform and cause pain for the child. This article reviews each collection method, and describes collection procedures, indications and strategies to optimise success and reduce contamination.

INTRODUCTION

Urinary tract infections (UTI) are one of the most common bacterial infections of early childhood. Among the many febrile young children who present for medical care, approximately 7% will have a UTI.[1] Complications of paediatric UTI are uncommon, but can be serious when they occur, including sepsis, meningitis and permanent renal scarring.

UTI in young children cannot be diagnosed reliably without a urine sample. However most young children do not achieve urinary continence until 2–3 years of age in Western society, so collecting urine samples from young children can be challenging.

WHO NEEDS A URINE SAMPLE

Signs and symptoms of UTI in young children are often non-specific. Features such as fever, poor feeding, lethargy and vomiting overlap with many common and benign viral infections, as well as serious bacterial infections. Localising signs such as dysuria (lower UTI: cystitis) or flank pain (upper UTI: pyelonephritis) are uncommon. Clinical diagnosis of UTI in young children is unreliable, so many febrile young children need a urine sample to diagnose or exclude UTI.

Before starting empiric antibiotics for suspected UTI, a urine sample should be collected to confirm the diagnosis.

A urine sample should also be collected from young children with fever without focus, especially if the child is a neonate, younger infant or unwell. Outside early infancy and if the child is not unwell, it may be reasonable to wait 24 hours to see if a focus emerges,[2] and if not, then check the urine.

In general, children with a clear alternative focus of illness do not need a urine sample.[2] Exceptions include the full septic workup for sick young infants, the child with predisposing features such as renal tract anomalies, the child vulnerable to UTI complications such as solitary kidney and the child with an alternate focus not following the expected course.

WHAT IS THE URINE SAMPLE USED FOR

Dipstick and microscopy screening

Urine dipstick testing is a fast and cheap bedside screening tool. Small chemical reagent squares change colour in the presence of specific substrates. Screening for UTI includes checking for nitrites and leucocyte esterase. Urinary nitrites are produced by most but not all uropathogenic bacteria, which convert dietary nitrates into urinary nitrites. Nitrites are highly specific, but not fully sensitive, for UTI. Leucocytes (white blood cells) commonly appear in the urine in response to UTI, but sterile pyuria also occurs with other infections.[3] Leucocyte esterase (an enzyme present in leucocytes) is also neither fully sensitive or specific for UTI. Dipstick screening is less reliable in younger infants, as frequent voiding flushes nitrites and leucocytes out of the bladder. While not diagnostic nitrites and leucocytes, particularly when used in combination, are a handy screening tool

to indicate if UTI is likely, and to guide initial management.[2 3]

Urine microscopy can also identify leucocytes and bacteria in the urine, augmenting dipstick screening.

Culture

The gold standard for UTI diagnosis is laboratory urine culture. All major international guidelines recommend culture is used to diagnose UTI in young children.[2 4–6] Urine is added to an enriched medium, and considered positive if bacteria grow in sufficient quantity. Results take around 24 hours, at which point the presumptive dipstick diagnosis should be reviewed. Identifying the uropathogen, and its antibiotic sensitivities, guides targeted antibiotic therapy. How much growth on culture is required to diagnose UTI, the colony forming units count, varies between collection methods and local guidelines.[4–6] Bacterial growth at lower counts or without pyuria may suggest asymptomatic bacteriuria, contamination or early infection.

CONTAMINATION

Contamination is a dirty word when it comes to evaluating UTI. Contamination generally refers to mixed growth of multiple bacterial species. Assuming UTI is caused by a single uropathogen, multiple organisms suggests contamination with incidental skin flora. Contamination corrupts the culture result, as mixed growth may be entirely skin flora, or may conceal a true uropathogen. Incidental skin flora can also lead to false-positive UTI diagnosis if a single species dominates the culture.

Contamination can occur when urine flushes the vagina or glans and foreskin on voiding. Cleaning before collection can reduce the burden of incidental skin flora, although cleaning practices vary. Gauze and sterile water and/or soap may be sufficient for non-invasive collection, but antiseptic cleaning is required before invasive procedures.[5]

Avoiding contamination is crucial when investigating UTI. For nappy pads and urine bags around half the cultures can be contaminated.[7 8] Contamination does not affect dipstick screening, or urine protein and metabolic tests. Differences in how laboratories define contamination (and UTI) can limit comparing contamination rates between different studies and collection methods, although one study has compared contamination between methods at a single centre (table 1).[7]

INVASIVE VERSUS NON-INVASIVE COLLECTION

Young children who are not yet toilet-trained cannot void on demand to provide a midstream sample of urine. When facing a febrile precontinent child, other collection methods are required (figure 1).

Non-invasive methods involve waiting for spontaneous voiding, then opportunistically collecting urine in a nappy pad or bag, or 'clean catch' of the urine stream. These methods seem convenient and can be done at home by parents, but can be time-consuming, unsuccessful or contaminated. Invasive methods extract urine directly from the bladder by urethral catheterisation or suprapubic needle aspiration (SPA). In skilled hands these methods can be more reliable, but require expertise and equipment to perform, and cause pain and distress to the child.

The optimal collection method remains controversial. All collection methods have advantages and

Table 1 Urine sample collection methods for young precontinent children

Method	Advantages	Limitations
Non-invasive collection methods		
Nappy pad	Convenient. Can be used for dipstick screening.	Very high contamination: >60%.[11] Not reliable for culture.
Urine bag	Convenient. Can be used for dipstick screening.	High contamination ≈50%.[7 8] Not reliable for culture.
Clean catch	Least contamination of non-invasive methods.	Moderate contamination: ≈25%.[7] Can be time-consuming.
Voiding stimulation for clean catch methods		
Bladder-lumbar method	Increases success of clean catch. Effective in neonates.	Requires two to three operators. May be difficult in older infants.
Quick-Wee method	Increases success of clean catch. Simple, single operator.	Moderate contamination: ≈25%.[19]
Invasive collection methods		
Catheterisation	Low contamination ≈10%.[7] Effective even if little urine in bladder. Reliable to confirm UTI.	Expertise and equipment required. Painful and invasive for the child.
Suprapubic aspiration	Very low contamination ≈1%.[7] Can increase success with ultrasound. Very reliable to confirm UTI.	Expertise and equipment required. Painful and invasive for the child.

UTI, urinary tract infection.

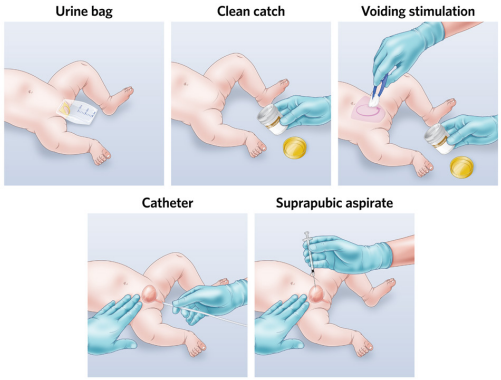


Figure 1 Common urine collection methods for young precontinent children. Images by Dr Jonathan Kaufman and Bill Reid, Royal Children's Hospital.

limitations. Accordingly, clinicians and parents have different preferences, and guidelines have different recommendations.[2 4]

The National Institute for Health and Care Excellence (NICE) UK Guidelines recommend the clean catch method.[2] If clean catch is not possible, other non-invasive methods are recommended. Invasive methods are only suggested where non-invasive methods are not possible or practical. In contrast, the American Academy of Pediatrics US Guidelines recommend the opposite, recommending catheter or SPA collection due to lower contamination.[4] Non-invasive methods are suggested only for dipstick screening, with invasive collection required to confirm positive screening. Why do these major guidelines have opposing recommendations? Mostly for practical reasons. In the UK, primary care for children is provided by general practitioners who are unlikely to perform invasive collection procedures, while in the USA it is often provided by paediatricians. And elsewhere? Most European guidelines recommend clean catch but acknowledge catheter and SPA as the reference standard, and discourage bag collection except for screening because of contamination (table 2).[6 9 10] Australian guidelines recommend clean catch for children who are not too unwell, catheter or SPA for sick infants and discourage sending urine bag for culture.[5]

CHOOSING YOUR COLLECTION METHOD

Suboptimal sample collection is detrimental to both patient care and health service efficiency. Delayed sample collection increases healthcare resource use. Missed sample collection increases the likelihood of both missed diagnosis and misdiagnosis, which may in turn increase inappropriate antibiotic prescribing and antimicrobial resistance. Optimising sample collection has many benefits.

Choosing the optimal collection method for your patient balances time, equipment, expertise, invasiveness and the likelihood of success and contamination (table 1). In younger and sicker children, an invasive sample is often required to minimise contamination and delay. In older and less unwell children, a clean catch sample may be sufficient. Bag collection is convenient for screening, but false positives and contamination

Table 2 International guideline recommendations for urine sample collection for UTI in young precontinent children

Guideline	Recommendations
National Institute for Health and Care Excellence, UK[2]	► **Clean catch recommended method.** ► If clean catch unobtainable, use other non-invasive methods. ► Do not use cotton wool balls, gauze or sanitary towels. ► Catheter or SPA if non-invasive methods not possible or practical.
American Academy of Pediatrics, USA[4]	► **Catheter or SPA sample required to diagnose UTI.** ► Can use convenient sampling to obtain urine for screening. ► Must confirm positive screening with culture from catheter or SPA.
European Association of Urology/European Society for Paediatric Urology[24]	► **Clean catch, catheter and SPA recommended methods.** ► **SPA method of choice due to least contamination.** ► Bag specimens can be used for screening.
Italian Society for Paediatric Nephrology[6]	► **Clean catch recommended method.** ► **Catheter recommended for severely unwell children.** ► Bag specimens can be used for screening.
French Pediatrics Society[10]	► **Clean catch, catheter and SPA recommended methods.** ► Bag specimens cannot be used to confirm UTI.
Dutch Association for Pediatrics (The Netherlands)[9]	► **Clean catch or catheter recommended methods.** ► Bag specimens can be used for screening.
Spanish Association of Paediatrics (Spain)[25]	► **Catheter or SPA recommended methods.** ► Bag and clean catch useful for screening. ► Bag specimens should not be sent for culture.
Victorian Statewide Clinical Practice Guidelines (Australia)[5]	► **Clean catch appropriate if child not severely unwell.** ► **SPA is gold standard.** ► Bag specimen not recommended for culture.

SPA, suprapubic needle aspiration; UTI, urinary tract infection.

make culture results unreliable. Contamination is a crucial consideration.

NAPPY PADS AND COTTON WOOL BALLS

Nappy pads are non-invasive and seemingly convenient. Pads are placed inside the nappy, and urine extracted with a syringe after the child voids. However, nappy pads have the highest contamination of all collection methods, reported at over 60% in some settings.[11] This is understandable, as they are in close continuous contact with the perineal skin. High contamination makes culture from pad samples highly unreliable.

Cotton wool balls have similar problems with high contamination, and are specifically discouraged by NICE guidance.[2]

URINE BAGS

Urine collection bags are another seemingly convenient non-invasive method. The bag is attached over the genitalia with gentle adhesive. They can be placed inside the nappy, or the nappy slit to visualise the bag. They can sometimes leak or detach, and minor discomfort and skin irritation can occur with removal. Average collection time was 85 min in one small observational study,[12] and success of bag collection is reported as 82%–96%.[12 13]

High contamination also makes culture from urine bags unreliable. Like pads, bags are in close contact with the perineal skin. A systematic review including 7659 bag samples from 21 studies found a pooled percentage of 46.6% contamination and 61.1% false positives.[8] Many guidelines specifically recommend against sending bag samples for culture due to high contamination.[4–6 10] Bag specimens may be helpful for dipstick screening and ruling out UTI, but if positive a more reliable sample should be collected for culture confirmation.[4 6]

CLEAN CATCH

Clean catch is a commonly favoured non-invasive method, and recommended in many guidelines including NICE.[2 5 6] Remove the nappy, clean the skin and wait for the child to void spontaneously. Careful attention and quick reflexes are required to catch a sample when they do. The catching task often falls to the parents: a challenge in the middle of the night with a sick child.

Clean catch is not perfectly clean, but has the lowest contamination of non-invasive methods, reported around 10%–25% in most studies.[7 11] Take care to minimise contamination. Collectors must avoid touching the inside of the specimen jar, or touching the jar against the child's skin. While collecting midstream urine is recommended in continent patients to reduce contamination, in precontinent children collecting a definite midstream specimen is difficult.

Clean catch is not always caught, and can be time-consuming. The median time for clean catch attempts in an emergency department (ED) setting is 30 min, with a 64% success rate.[14] Most successful clean catches will happen within an hour—after an hour the likelihood of success plateaus significantly.[14]

So what can be done to expedite clean catch? Offering hydration to increase urine output, and voiding stimulation methods, can increase success.

VOIDING STIMULATION METHODS FOR CLEAN CATCH

Voiding stimulation methods trigger newborn cutaneous voiding reflexes and involuntary urination. Anecdotally, many parents know that changing a nappy often triggers voiding, and many clinicians know that skin cleaning before catheter or SPA procedures can have a similar effect. This suprapubic stimulation triggers reflex parasympathetic bladder contraction. Two voiding stimulation methods have been shown to be effective in clinical trials: the bladder-lumbar stimulation method, and the Quick-Wee method. Most studies evaluate a 5 min stimulation period.

A finger-tap bladder stimulation method to obtain urine samples from babies was first described in 1985, tapping above the pubic symphysis at a rate of one tap per second.[15] The subsequently described bladder-lumbar stimulation method uses combined bladder and lumbar stimulation manoeuvres to trigger voiding.[16] The baby is held suspended under the armpits with legs dangling, while a second operator applies alternating 30 s stimulation with suprapubic bladder tapping and lumbar circular massage. Success obtaining urine in the neonatal setting is high. In the ED setting, non-randomised trials evaluating a 5 min time period report success of 27% for infants over 1 month of age,[17] and 49% for infants 0–6 months of age.[18] Maintaining the child's position can be difficult in older and heavier infants.[17]

The Quick-Wee method uses cold fluid-soaked gauze to gently rub the suprapubic area in circular motions with the child in the supine position (figure 1) (see online supplementary video).[19] The simple single operator method can be performed by doctors, nurses or parents. In a large randomised trial for infants aged 1–12 months, 31% voided within 5 min with Quick-Wee, compared with 12% with standard clean catch, with high parent and clinician satisfaction.

Like other newborn reflexes, cutaneous voiding reflexes diminish with age as volitional bladder control develops, so voiding stimulation methods are more effective in younger infants and in the first year of life.[17 18]

CATHETERISATION

Catheterisation involves inserting a catheter (or feeding tube) through the urethra into the bladder, which is removed once urine is obtained, also known as an 'in-out catheter' (table 3). Appropriate training and experience is required. Success varies with the

Table 3 Invasive collection procedures

Catheter	
Positioning	
Female	
Male	
	Indications Urgent and/or sterile urine sample collection. **Contraindications** Anatomical obstruction (eg, labial fusion, hypospadias). **Advantages** Low contamination: 10%. Can be effective even with low bladder volume. **Risks** Common: microscopic haematuria, dysuria. Very rare: urethral injury. **Equipment** 6 Fr enteral feeding tube or catheter, 5 mL syringe, lubricant gel. Dressing pack with gauze and sterile paper sheet/drape. Topical antiseptic wash (eg, dilute chlorhexidine). Sterile urine jar and sterile gloves. **Analgesia** Oral sucrose (<6 months). No benefit of intra-urethral anaesthetic gel over lubricant gel. Consider age-appropriate sedation if >1 year of age (eg, nitrous, midazolam). **Preparation** Assistant holds child supine with legs in frog-leg position. Hold or wrap child's arms. Child may void with preparation—have jar ready for catch. **Procedure** Identify urethral orifice and clean area. Create sterile field with hole in centre of paper drape. 'Dirty' hand to touch patient, 'clean' hand to hold catheter. Lubricate catheter tip, insert catheter. Gently manipulate/rotate to advance into bladder, do not force. Discard first few drops of urine if possible (contamination). Allow urine to drip from end of catheter into sterile jar. If urine not flowing, can use syringe to aspirate. **Practice points** Use clean pieces of gauze to hold penile shaft/spread labia. May require gentle pressure to advance through bladder neck. Boys: may need gentle traction or change of angle of penile shaft, do not force retraction of non-retractile foreskin. Girls: if catheter inserted into vagina, leave in situ, aim superiorly with second catheter. Children >1 year of age may require larger catheter size, eg, 8 Fr 1–3 years of age. Ensure correct bed height and adequate lighting for procedure.

Continued

Table 3 Continued

Suprapubic needle aspiration[5]

Positioning	
Landmarks	
Needle insertion	

Indications
Urgent and/or sterile urine sample collection.
Child <2 years of age.
Contraindications
Overlying skin trauma or infection.
Risk of bleeding (eg, thrombocytopaenia, coagulopathy).
Abdominal distension or intra-abdominal organ anomalies.
Advantages
Lowest contamination of all collection methods: 1%.
Risks
Common: microscopic haematuria, minor bruising.
Very rare: bowel perforation, major bleeding.
Equipment
23 gauge needle, 5 mL syringe, sterile gloves.
Topical antiseptic wash (eg, dilute chlorhexidine) or alcohol swab.
Sterile urine jar.
Analgesia
Oral sucrose (<6 months).
Topical anaesthetic cream (unless urgent procedure).
Preparation
Ensure adequate bladder volume.
Assistant holds child supine with legs extended.
Hold or wrap child's arms.
Child may void with preparation—have jar ready for catch.
Procedure
Identify insertion point: suprapubic crease, midline.
Clean skin.
Insert needle at 90° to skin.
Use smooth quick motion to penetrate skin and bladder.
Advance to hub, aspirate.
If no urine, continue aspirating while slowly withdrawing needle.
If no urine, withdraw to just below skin, redirect slightly superiorly ×1 further aspiration attempt.
When urine aspirated, remove needle, syringe urine into sterile jar.
Practice points
Low success rate if little urine in bladder.
Ultrasound to confirm bladder volume >2 cm recommended.
Otherwise ensure no wet nappy in preceding 30–60 min.
Optimise hydration if bladder volume insufficient.
Catheter recommended if failed suprapubic needle aspiration or low bladder volume.

operators level of experience, reported between 68% and 100%.[20 21]

Contamination with catheterisation is low, at around 10%.[7] Discard the first few drops of urine (when possible) to replicate midstream collection and reduce contamination.[4] Catheterisation can be successful even with little urine in the bladder, so can be considered after other failed collection attempts.

Catheterisation is invasive and therefore painful. Use age-appropriate procedural analgesia or sedation, although intraurethral anaesthetic gel is no better than non-anaesthetic lubricant for pain reduction.[22] The catheter may require some gentle manipulation, but should never be forced. Minor complications such as self-limiting haematuria and dysuria are not uncommon, while serious urethral injury is very rare.

SUPRAPUBIC NEEDLE ASPIRATION

SPA involves inserting a needle into the bladder through the skin of the lower abdomen, and aspirating urine (table 3). SPA is appropriate for children <2 years of age. Appropriate training and experience is required, although the procedure is quite straightforward once learnt. Success varies with operator experience and volume of urine in the bladder, but is reported as 46%–90%.[20 23] Do not remove the nappy until someone with a urine jar is ready for an opportunistic clean catch.

Contamination with SPA is ultra-low, at only 1%.[7] Identifying adequate bladder volume with bedside ultrasound before SPA increases success and is recommended,[2] although automated bladder scanners are unreliable in infants. Needle insertion does not require ultrasound visualisation. Blind SPA without ultrasound can be performed, but if the child has recently voided, the bladder volume is likely to be low.

SPA is invasive and therefore painful. Use topical anaesthetic cream when possible. Minor haematuria and bruising is relatively common, but serious complications such as needle insertion into the bowel are very rare. Suprapubic abscess, haemoperitoneum and anaerobic bacteraemia have been reported in case reports.

WHAT TO DO IF UNSUCCESSFUL

Collection attempts are not always successful. Try again, wait, offer fluids to optimise hydration or repeat voiding stimulation. Consider time-limiting non-invasive attempts then trying another method (eg, clean catch is unlikely to be successful after an hour, but catheterisation can be successful even with very little urine in the bladder).

Sometimes collection is unsuccessful despite everyone's best efforts. Re-evaluate the need for urine collection: has an alternate focus become apparent? The septic infant will require admission, but willing parents can be given provisions to continue clean catch at home for the more well child. Urine samples can be refrigerated once collected, and follow-up arranged if the child remains well.

CONCLUSION

Collecting urine samples from young children can be challenging. All collection methods have advantages and limitations. Pads and bags have high contamination, so can be used for dipstick screening but culture will be unreliable. Clean catch has the lowest contamination of non-invasive methods and is recommended by NICE guidelines, but can be time-consuming. Clean catch success can be optimised with voiding stimulation methods such as bladder-lumbar stimulation or Quick-Wee. Catheter and SPA can be effective and have lower contamination, but are invasive procedures that require expertise and cause pain for the child. There is no single approach for every patient, clinician or setting, so consider which is best suited, and remember sometimes you just have to go with the flow.

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Clinical Intelligence

Jonathan Kaufman, Meredith Temple-Smith and Lena Sanci

Urine sample collection from young pre-continent children:

common methods and the new Quick-Wee technique

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BACKGROUND

Urinary tract infections (UTIs) are one of the most common bacterial infections of early childhood. However, as signs and symptoms are frequently non-specific in young children, a urine sample is required to diagnose or exclude UTI. National Institute for Health and Care Excellence (NICE) guidelines recommend that children with unexplained fever or signs suggestive of UTI should have a urine sample collected.[1]

Collecting urine from pre-continent children is challenging. Collection methods all have limitations. The choice of sample collection method must balance time, resources, contamination, invasiveness, and clinician and carer preferences. Despite being so commonly required for young children, there is significant variation in international guideline recommendations for the optimal method. NICE recommends the clean catch method, other non-invasive methods such as pads if clean catch is not possible, and catheter or suprapubic aspirate (SPA) if non-invasive methods are not possible.[1]

Sample contamination occurs when urine flushing over the perigenital skin collects incidental skin flora, or from inadvertent contact between skin and specimen jar. Contamination corrupts the test result. Precise contamination rates for each method of urine collection may be difficult to compare as definitions of contamination vary between centres and studies. However, perigenital skin cleaning before collection and care with collection technique may help to minimise contamination.

Suboptimal sample collection is detrimental to patient care. A lack of timely, accurate sampling may delay effective treatment. Missed sample collection increases the likelihood of both missed diagnosis and misdiagnosis, which may in turn increase inappropriate antibiotic prescribing and antimicrobial resistance. Optimising sample collection has many benefits.

We present an overview of common urine sample collection methods used for young pre-continent children that can be considered for use in primary care (Figure 1 and Table 1).

NON-INVASIVE COLLECTION METHODS

Non-invasive collection methods involve waiting for the child to void spontaneously and then collecting urine with a urine bag, pad, or clean catch of the urine stream. These methods seem convenient, but can be time consuming, unsuccessful, or contaminated. Newer voiding stimulation techniques may improve the speed and success of non-invasive collection.

Nappy pads and cotton wool balls

Nappy urine collection pads are placed inside the nappy until the child voids. Urine can then be extracted from the wet pad with a syringe. Frequent checking is required to avoid faecal soiling. Nappy pads have the highest contamination of all urine collection methods,[2] reported at >60% in some primary care settings.[3] Continuous contact between pad and perineum makes avoiding contamination difficult, even with meticulous care. Cotton wool balls placed in the nappy

Figure 1. Common urine sample collection methods.
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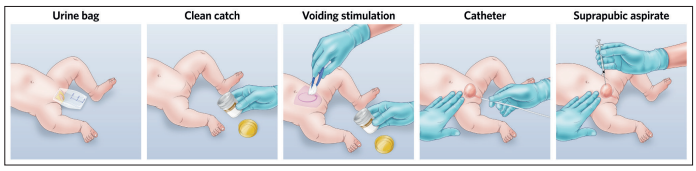


Table 1. Advantages and limitations of common methods

Method	Advantages	Limitations
Nappy pad	Convenient Can be used to exclude UTI	Very high contamination: >60%[3] Unreliable to confirm UTI
Urine bag	Convenient Can be used to exclude UTI	High contamination: ≈50%[4] Unreliable to confirm UTI
Clean catch	Can increase success with voiding stimulation More reliable than pad/bag to confirm UTI	Moderate contamination: ≈25%[5] Can be time consuming or unsuccessful
Catheterisation	Low contamination: ≈10%[5] Effective even if little urine in bladder Very reliable to confirm UTI	Equipment and expertise required Invasive and painful for the child
Suprapubic aspiration	Ultra-low contamination: 1%[5] Can increase success with ultrasound Very reliable to confirm UTI	Equipment and expertise required Invasive and painful for the child

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Provenance

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are sometimes used in a similar fashion, but are specifically discouraged by NICE guidance.[1]

Urine bags

Urine collection bags are attached with gentle adhesive over the child's genitalia. They are placed inside the nappy, or the nappy can be slit to visualise the bag. While seemingly convenient, bags can leak or detach, so care with collection is still required. Discomfort and skin irritation with bag removal may occur, but is usually minor. Urine collected in bags is also highly susceptible to contamination. A meta-analysis of 21 studies (7659 samples) found 47% contamination and 61% false positives with urine bags.[4]

Clean catch

The clean catch method for pre-continent young children replicates the midstream technique used in continent older children and adults. The nappy is removed, and a clinician or carer waits with a specimen jar, ready to opportunistically catch a sample when the child voids. Vigilance and quick reflexes are required. This can sometimes be difficult and time consuming, and not all attempts are successful. Clean catch has the lowest contamination of non-invasive methods for pre-continent children, at around 25%.[5]

Voiding stimulation techniques

Voiding stimulation techniques trigger involuntary newborn voiding reflexes, to facilitate faster clean catch urine collection. Bladder–lumbar stimulation involves suspending the infant under the armpits and applying alternating bladder tapping and lumbar massage.[6] Success is high in newborns, but three operators are required and it may be less practical in older infants. The Quick-Wee method uses cold fluid-soaked gauze to gently rub the suprapubic area.[7] The method is simple, gentle, and can be performed by a single operator, being the doctor, nurse, or parent. Thirty per cent of children <1 year old had a sample collected within 5 minutes in a large randomised trial.[7] If not successful, waiting for a clean catch should be continued and optimising hydration or trying stimulation again later considered.

INVASIVE COLLECTION METHODS

Invasive collection methods involve urethral catheterisation or suprapubic needle aspiration to sample urine directly from the bladder. These methods can be more reliable, but require equipment and expertise to perform, and cause pain to the child and distress to parents.

Catheterisation

Catheterisation involves inserting and removing a catheter or feeding tube into the bladder via the urethra. This can be effective even with scant urine in the bladder, and has low contamination of around 10%.[5]

Suprapubic aspiration

SPA uses a needle and syringe to sample urine through the abdomen and bladder wall. Success is higher with a full bladder, preferably confirmed with ultrasound, or suggested by an absence of recent voiding. SPA contamination is around 1%, the lowest of all collection methods.[5]

DISCUSSION

Pads and bags are often favoured collection methods in primary care and seem convenient, particularly for parents collecting samples at home. High contamination and false positive rates, however, limit their diagnostic utility. Pad and bag urine samples therefore may be useful for dipstick screening or to exclude UTI if culture results are negative, but positive results must be interpreted with caution. Positive screening should be confirmed with a more reliable sample if possible.

Catheter and SPA procedures are invasive and more commonly performed in the hospital setting, but have lower contamination than other methods. These methods may also be useful in geographically isolated primary care settings.

Clean catch is recommended by NICE and has the lowest contamination of non-invasive methods. Motivation and attention is required for a successful catch, so parental engagement is crucial. Voiding stimulation techniques such as the Quick-Wee method are simple and can increase success. We have created a parent education handout to assist with clean catch collection at home, which may be helpful for clinicians (see Supplementary Figure 1).

CLEAN CATCH URINE COLLECTION FOR YOUNG CHILDREN

Your child needs a urine (wee) sample collected. This can sometimes be difficult with young children who aren't yet toilet trained (and can't wee on demand).

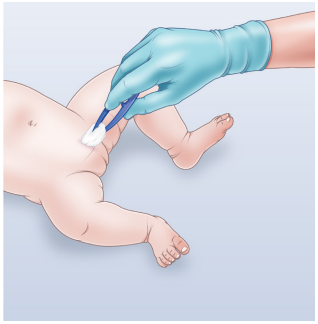
Your nurse or doctor has recommended collecting a sample using the Clean Catch method.
This involves waiting for your child to wee, and catching some urine when they do.
Gently rubbing the lower abdomen with cold wet gauze can trigger a wee and speed up collection.

WHAT EQUIPMENT IS NEEDED:

- sample container
- gauze and water, or baby wipes

PREPARING FOR A CLEAN CATCH:

- offer your child a drink (breastfeed, bottle, cup)
- wash your hands, or wear disposable gloves, and open the sample container



1. CLEAN

- remove your child's nappy, clean around the genital area with gauze soaked in water
- if you don't have any gauze, use baby wipes



2. RUB

- gently rub the lower abdomen (tummy) with clean gauze soaked in cold water
- this often triggers a wee:
  rub for a few minutes, if no wee you can try again later



3. CATCH

- keep waiting and be ready to catch a sample in the container when your child wees
- screw the lid on tightly and return it to your nurse or doctor

AVOIDING SAMPLE CONTAMINATION:

Don't hold the sample container against your baby's skin
Don't touch the inside of the sample container.
This is important so that bacteria from the skin don't contaminate the sample.

This handout contains general information and should be used in conjunction with the advice of your nurse or doctor.
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Developed by Dr Jonathan Kaufman, supported by the Department of General Practice, The University of Melbourne. © 2019

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11.1.4 Paper 9

Jonathan Kaufman, Shidan Tosif & Trevor Duke (2017) Voiding stimulation methods for collecting urine from young pre-continent children, Paediatrics and International Child Health, 37:4, 298-299, DOI: 10.1080/20469047.2017.1399650

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Letter to the Editor

Voiding stimulation methods for collecting urine from young pre-continent children

We read with much interest the recent review by Korbel *et al*. on the diagnosis and management of paediatric urinary tract infection (UTI) [1]. We wish to highlight the potential of voiding stimulation techniques to address the challenge of urine sampling in young pre-continent children, particularly in resource-limited settings.

The authors draw attention to UTI as a common cause of febrile illness in childhood, with a peak incidence in pre-continent children. Previous reports have indicated that UTI affects 7% of febrile children under 2 years of age, [2] and up to 9% in low- and middle-income regions [3]. The prevalence may be even higher in febrile malnourished children [4]. As mentioned, the signs of UTI in younger children are often non-specific. In the differential diagnosis of febrile young children, UTI is often acknowledged as a possible source but might be ignored because the specimen collection technique is too difficult or invasive.

The authors highlight that diagnosis of UTI requires positive laboratory testing, ideally for culture confirmation. Dipstick urinalysis and urine microscopy may also assist diagnosis or exclusion, especially in the resource-limited setting [5]. Collecting a urine sample from a young pre-continent child, however, can be very difficult. The World Health Organization Pocketbook of Hospital Care for Children and the UK National Institute for Health and Care Excellence guidelines suggest collecting a “clean catch” urine (CCU) sample if possible [5,6]. CCU is non-invasive but can be time-consuming or unsuccessful [7], particularly in children who are unwell and dehydrated. As noted, urine cultured from bag

specimens have unacceptably high contamination rates. Suprapubic aspiration (SPA) may be required for sick infants [5], and SPA or catheter collection have less contamination, but these methods are invasive and require technical expertise and equipment. These challenges in collecting urine samples mean that the diagnosis of UTI is often missed or delayed. The ideal method of sample collection would be non-invasive, fast, gentle and simple.

Voiding stimulation techniques may improve CCU collection to investigate UTI, especially in resource-limited settings where SPA and catheter collection are impractical. These techniques trigger involuntary newborn cutaneous voiding reflexes which are present at birth but diminish with age. The 'Quick-Wee' method involves using gauze soaked in cold fluid to gently rub the suprapubic area [8]. In a randomised controlled trial in the paediatric emergency department, this method was found to trigger voiding and successful CCU collection within 5 minutes in 30% of infants aged 1–12 months compared with 9% using standard CCU [9]. Where cold fluid is not available, a smaller non-randomised study found room temperature fluid was effective for 25% of infants [8]. Lumbar bladder stimulation is another voiding stimulation technique: the infant is suspended under the armpits while repetitive lumbar and bladder stimulation is performed by a second operator [10]. A randomised trial in newborns who were not unwell or dehydrated had a 5-minute success rate for CCU in 78% of neonates within 5 minutes compared with 33% without stimulation [11]. In subsequent non-randomised studies of older infants in the emergency department, lumbar bladder stimulation had a 5-minute CCU collection rate of 27–49% and it was more likely to succeed in infants under 3 months of age [12,13].

Voiding stimulation techniques can improve the speed and success of CCU collection to evaluate potential UTI in febrile young children. Faster sample collection allows the clinician either to reach the diagnosis and instigate treatment or to exclude the diagnosis and

look for another source of infection. Both methods require minimal resources and are a pragmatic way of improving CCU collection from young pre-continent children.

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FOCUS

Childhood constipation



Michelle Waterham, Jonathan Kaufman, Susan Gibb

Background

Constipation is best defined as difficulty passing stools that may be infrequent (≤2 per week), painful and associated with stool retention. Childhood constipation is common, with a prevalence of 3–30% worldwide. Most constipation in children is functional and related to behavioural withholding after an unpleasant stool event. Successful diagnosis and management can occur in primary care, and specialist referral is only needed for refractory cases or concerns regarding organic pathology.

Objectives

This article aims to provide a structure for evaluating, diagnosing and managing childhood functional constipation in general practice.

Discussion

Structured history and examination can screen for organic pathology or red flags that require specialist referral. Investigations such as abdominal X-ray are not routine. Early management of childhood constipation provides improved quality of life for patients and their families. Management, including disimpaction and maintenance, should maintain continuity of care and provide long-term support for families.

Constipation is a common problem in childhood, affecting an estimated 3% of children worldwide and up to 30% in some settings.[1–3] There is a degree of variability in the expected frequency of stools in healthy children; however, most children pass stools every two to three days, whereas breastfed babies may only pass stool once a week. Constipation is defined as the infrequent passage of stools (≤2 per week) with associated stool retention, and possible painful bowel actions or overflow faecal incontinence and soiling (encopresis). 'Functional constipation' describes constipation that does not have an organic aetiology.[4]

Constipation in children is usually functional or idiopathic, and related to behavioural withholding after a painful or unpleasant stool event. Stool builds up within the colon and rectum, leading to the absorption of water and, therefore, accumulation of hard faecal matter.[5] This faecal retention stretches the lower bowel and rectum. Over time, the sensation of 'needing to go' when the rectum is full diminishes with persistent rectal stretching from chronic stool loading. This rectal hyposensitivity can lead to involuntary soiling and will persist until chronic stretching is alleviated and prevented from recurring. Soiling can be embarrassing and distressing.

Treatment needs to first disimpact hard stool from the bowel, then maintain ongoing soft stools. A supportive and long-term outlook to treatment over months is required. Successful management of childhood functional constipation in primary care will have a significant positive impact for children and families, and be very rewarding for clinicians.

History

Key features to ask about are the stool frequency and consistency using the Bristol stool form scale (Figure 1),[6] precipitating factors (eg painful stool events, behavioural toileting refusal), faecal soiling, and the presence of any red flags that suggest serious organic pathology (Table 1). Childhood functional constipation is best described using the Rome IV criteria and is defined by the presence of two or more of the following features for at least one month:[5,7–9]

- ≤2 stools per week
- excessive stool retention

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- painful or hard bowel movements
- presence of large faecal mass in rectum
- history of large diameter bulky stools
- >1 episode per week of faecal incontinence after toilet training completed.

While the median age for onset of functional constipation is 2.3 years,[5] common times for constipation to arise include transition to solids, toilet training and school entry. Other precipitants to investigate include painful bowel actions leading to withholding behaviour (eg perianal skin conditions, anal fissures), toileting refusal, change of diet and psychosocial stressors.

The Bristol stool form scale (Figure 1) allows a reproducible, subjective assessment of stool consistency,[6] and the chart is freely available online from the Royal Children's Hospital's *Constipation clinical practice guideline*.[10] A Bristol type 3 or 4 stool every day or every second day is the goal. When constipated, there may be hard stools (types 1–2); if there is retained impacted stool, there may be watery overflow diarrhoea (types 6–7).

Dietary factors, including inadequate fibre and water intake, are rarely the primary cause of constipation but may contribute. Ask about other medications (eg anticholinergics), previous laxative use, and their duration and effect.

Organic disorders are uncommon, but consider the possibility of coeliac disease or cow's milk protein allergy if the history is suggestive. The presence of red flag symptoms (Table 1), such as urinary incontinence in a previously continent child, should prompt specialist referral.

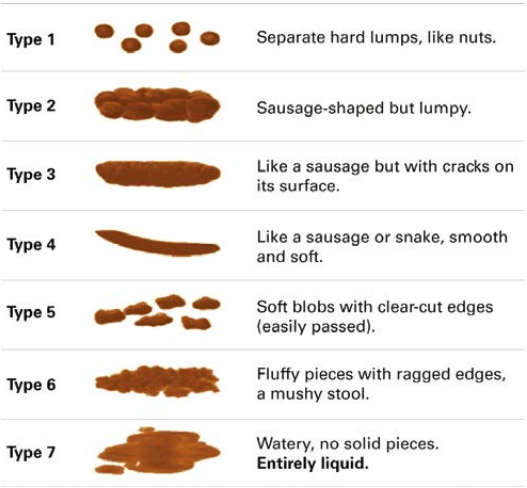


Figure 1. Bristol stool form scale[6]

Examination

A general examination should include recording the current growth parameters and centiles (ie height, weight, head circumference), compared with previous records, to check for faltering growth trajectory and failure to thrive. A targeted abdominal examination should check for distension, bowel sounds and palpable stool. The spine and sacrum (to exclude hair patches, sacral pits, scoliosis), and lower limbs (muscle bulk, tone, power, reflexes of the lower limbs or functional testing in younger children) should be examined for features that suggest possible neurological aetiology. The perianal area should be examined for the anal orifice position, fissures and skin tags. Digital rectal examination is not routinely indicated in

Table 1. Childhood constipation key history and red flags

Constipation history key areas	
Stool frequency: <2 per week	
Stool consistency (using Bristol stool chart, normal is types 3–4)	
Painful bowel actions, straining, withholding behaviour	
Passing large, bulky stools	
Faecal incontinence and soiling	
Other precipitants: toileting refusal, psychosocial stressors, school entry	
Diet: introduction of solids, adequate fibre and water intake	
Other medications such as anticholinergics	
General growth and developmental progress	
Previous treatments: duration and effect/success	
Red flags for other disorders	
Failure to pass meconium <48 hrs after birth	Hirschprung's disease
Onset of constipation (from birth or first weeks of life)	Congenital, mechanical obstruction
Stool consistency (ribbon/pencil-thin stools)	Anorectal malformation
Bloody diarrhoea	Infection, inflammatory bowel disease, cow's milk protein allergy
Developmental delay	Metabolic or other
Lower limb neurology or urinary incontinence in older child	Spinal pathology
Other physical signs: lethargy, fever, bilious vomiting, rash	Infection, obstruction, metabolic

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children, as the history and abdominal examination is sufficient for evaluation of retained stool:[2] refer for specialist assessment if there are specific concerns.

Investigations

Investigations are not necessary if the history is consistent with functional childhood constipation. Full blood count and testing for coeliac disease, hypercalcaemia or hypothyroidism should be considered in cases of intractable constipation. Abdominal X-ray is not routinely indicated[2,3] and does not assist with the diagnosis of idiopathic or functional constipation. The history and physical examination of the abdomen provides sufficient clinical information regarding the presence of retained stool. Repeat X-rays are not required.

Treatment

Toileting behaviours and education

Education of appropriate toileting behaviour is essential for long-term success in the management of constipation. This should be seen as the main treatment, with the role of laxatives being to facilitate easy passage of stools. Reassurance may be required to alleviate parental anxiety. Resources for families and clinicians include the Royal Children's Hospital's *Constipation clinical practice guideline* and Kids Health Info Fact Sheets.

Children should be encouraged to sit on the toilet for five minutes after meals, up to three times per day. Parents should be advised about making toilet sitting a positive activity, with encouragement and support for the child.[11] Consider using a star chart to record progress (ie regular sitting, bowel actions, accidents, medications), which can be reviewed at follow-up appointments. Toilet sitting should be praised, even when no stool is produced. Children should sit with their feet supported and with their knees just above their hips – use a small stool or books to achieve this position. The child should straighten their back and bulge out their abdomen. For school-aged children, it may help to arrange for the child go to the toilet in the last period before lunchtime, or after eating, before playtime commences. A brief note or phone call to the child's teacher may assist in establishing this routine, and gather further information from the school environment that may be helpful.

Disimpaction

Disimpaction is often the first step needed to achieve treatment success, to remove the build-up of stool. This should be instigated where there is a history suggestive of chronic constipation and overflow soiling, with faecal loading on examination.[12] During disimpaction, families should be advised about what to expect, including elimination of the impacted faecaloma and a period of loose stools. PEG (polyethylene glycol) 3350 with or without electrolytes should be used for disimpaction (Table 2).[2,12–16] It is often helpful to keep school-aged children home from school for a few days (usually during second to fourth day of treatment) to achieve adherence and minimise the distress of increased soiling, or plan the disimpaction during school holidays. Aim for a watery, clear stool, which often takes up to a week of treatment to achieve. Parents may stop the disimpaction too early as the loose stools can be challenging to manage, so it is important to prepare them for the short-term inconvenience required for successful treatment.

Maintenance treatment

After disimpaction has been achieved (if required), maintenance therapy should be initiated (Table 3). Treatment effectiveness is defined by soft, spontaneous bowel actions most days of the week (Bristol types 3–4). There should be no faecal soiling or sense of urgency. Families should be advised to continue regular laxatives for at least two months, as premature treatment cessation often leads to recurrence within a few weeks. Titrate the dose to treatment effectiveness rather than ceasing too early. Educate families about the purpose of this extended duration of treatment, which is for the bowel to 're-learn' signals from the brain as to when the rectum is full. When the rectum has been chronically full, the signals have been switched off, and a period

Table 2. Childhood constipation disimpaction: First-line oral outpatient recommended regimen[20]

	PEG 3350 + electrolytes (paediatric/junior strength sachets) or PEG 3350 without electrolytes (small scoop)						
Age	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
1–12 months	1/2–1	1/2–1	1/2–1	1/2–1	1/2–1	1/2–1	1/2–1
1–6 years	2	4	4	6	6	8	8
6–12 years	4	6	8	10	12	12	12
	PEG 3350 + electrolytes (adult strength sachets) or PEG 3350 without electrolytes (large scoop)						
12–18 years	8	8	8	–	–	–	–

PEG, polyethylene glycol

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Table 3. Childhood constipation maintenance treatment guidelines[10]

Generic name	Mechanism of action	Maintenance dose	Disimpaction dose	Practice points
PEG 3350 or Macrogol 3350	• Iso-osmotic • Brings water into stool	• Aged 1–4 years – 1/2 scoop daily • Aged 4–5 years – 1 scoop daily • Aged 6–12 years – 1.5 scoops daily • Aged >12 years – 2 scoops daily	Refer to Table 2	• Can be added to any warm or cold drink • 1/2 scoop (8.5 g) • 1 scoop (17 g) • Virtually tasteless • Safe for long-term use • PBS-listed
PEG 3350 plus electrolytes or Macrogol 3350 plus electrolytes	• Iso-osmotic • Brings water into stool	• Aged 2–5 years – 1 half strength sachet daily • Aged 6–12 years – 1 sachet daily • Aged >12 years – 1–3 sachets daily	Refer to Table 2	• Full strength (13 g) • Half strength (6.9 g) • Salty taste • Safe for long-term use • PBS-listed
Paraffin oil	• Lubricant laxative	• Aged 1–6 years – 10–15 ml daily • Aged 6–12 years – 15–20 ml daily • Aged >12 years – up to 40 ml daily	NA	• Contraindicated in those with aspiration risk • Can stain underpants orange colour from oil
Lactulose	• Osmotic laxative • Brings water into stool	• Aged 6 months – 1 year – 5 ml daily • Aged 1–6 years – 5–10 ml daily • Aged >7 years – 10–15 ml daily	NA	• Can cause bloating/abdominal discomfort
Coloxyl drops	• Poloxamer • Assists mixture of water into stool	• Aged <6 months – 0.3 ml TDS • Aged 6–18 months – 0.5 ml TDS • Aged 18 months – 3 years – 0.8 ml TDS	NA	• Coloxyl + senna should be avoided unless stools are soft as senna is a stimulant
Sodium picosulfate drops	• Stimulant • Increases peristalsis in the gut	• Aged 4–10 years – 5–10 drops nocte • Aged >10 years – 10 drops nocte	NA	• Causes cramping if impacted • Drops are helpful if unable to swallow large volumes
Bisacodyl tablets	• Stimulant • Increases peristalsis in the gut	• Aged >10 years – 1–2 tablets (5 mg) nocte	NA	• Causes cramping if impacted
Sodium citrate/ sodium lauryl sulfoacetate/ glycerol enemas	• Osmotic laxative • Glycerol acts as lubricant	NA	NA	• Avoid when possible • 5 mL per rectum • Consider sedation with use

NA, not applicable; PBS, Pharmaceutical Benefits Scheme; PEG, polyethylene glycol

of regular soft stools are required for this re-learning. Use of simple language and a diagram may be helpful. Families are often concerned that the continuation of laxatives will lead to diarrhoea or dependence. It is important to reassure families that this should not occur if they use the appropriate dose and frequency.

Diet and food intolerance

Families often ask whether increased fibre or a change in diet will improve their child's constipation. While an increase in dietary fibre and adequate water intake may assist in improving stool consistency, this alone will be insufficient to resolve the condition.[17] It is uncommon for specific foods (eg dairy, wheat) to be contributing, but reassessment during treatment failure should be an opportunity to consider coeliac disease,[18] cow's milk protein allergy[19] or food intolerance.

Refractory constipation

If there are ongoing symptoms of constipation after six months of appropriate treatment, a referral for specialist care and a second opinion is warranted. Specifying chronicity and previous

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treatment measures in the referral letter can assist with prioritising referrals. Continue to monitor treatment while waiting for review, and aim to support families with long-term treatment as ongoing care may be required.

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ORIGINAL ARTICLE

Clean catch urine collection: Time taken and diagnostic implication. A prospective observational study

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Aim: Clean catch urine (CCU) collection is commonly used in pre-continent children. CCU can be time-consuming and specimens may be contaminated. Our aim was to determine the time taken for CCU attempts and to describe the success of this method in diagnosing or excluding urinary tract infection.

Methods: Prospective observational study of CCU in pre-continent children aged 2–48 months in the emergency department. Time taken until urine collection, 'successful' (voided and caught), 'missed' (voided not caught) or the procedure 'stopped', were recorded and urine culture results analysed.

Results: Two hundred and seventeen children (131 (60%) male) were enrolled. There were a total of 247 attempts at CCU. For the first attempt, the median collecting time was 30.5 min (interquartile range (IQR) 11–66). Outcome was 'successful' in 64% (95% confidence intervals (CI) 58–70%), 'missed' in 16% (95% CI 11–20%) and 'stopped' in 20% (95% CI 15–26%). Median time if 'successful' was 25 min (IQR 7–46.5), 'missed' 27 min (IQR 11.6–59) and 71 min (IQR 42.5–93) when 'stopped'. One hundred and sixty children had successful CCU collection, 129 were sent for culture. Fifty of 129 (39%) cultures were contaminated. If all urine specimens caught were sent for culture, the estimated yield of an uncontaminated urine specimen was 45%. Contamination was not related to time taken for CCU.

Conclusions: CCU is time-consuming, frequently unsuccessful and contaminated, resulting in a low overall diagnostic yield. Clinicians could expect a 45% chance of obtaining a definitive urine sample from this method overall.

Key words: emergency medicine; general paediatrics; nephrology/renal; urinary tract infection.

What is already known on this topic

1 Clean catch urine (CCU) is often the preferred method of urine specimen collection in pre-continent children, despite higher contamination rates than invasive methods.
2 The time taken waiting for CCU sample collection is unclear.
3 Little is known about the relationship between CCU collection time and contamination.

What this paper adds

1 CCU attempts are time-consuming.
2 CCU attempts have only a moderate success rate of obtaining a definitive sample.
3 Limitations of CCU are failure to void, missed catches and a high contamination rate.

Urinary tract infections are common in children under 2 years of age, and affect between 5 and 7% of febrile children without a focus in this age group.[1–3] Obtaining a urine specimen is frequently required to diagnose or exclude urinary tract infection (UTI), and is recommended for the young child who looks unwell,[4,5] particularly infants under the age of 6 months.[6]

A diagnosis of UTI requires a urine culture result of a sufficient bacterial colony count without evidence of contamination, and carries implications for treatment, follow-up and long-term morbidity.[7,8] The National Institute for Health and Clinical Excellence guidelines from the United Kingdom list clean catch urine (CCU) as the preferred method of urine collection for all children, unless a specimen is unobtainable by the CCU method.[6] In contrast, American Academy of Pediatrics guidelines state that convenient methods can be used to obtain a specimen for urinalysis, but for patients where antibiotics for potential or suspected UTI are to be commenced, a urinary catheter or suprapubic aspirate (SPA) specimen should be obtained for reliable diagnosis.[5] In younger children, both National Institute for Health and Clinical Excellence and American Academy of Pediatrics guidelines recommend that all urine samples should be sent for culture for definitive diagnosis of UTI.

CCU is often favoured for being less invasive and requiring less technical expertise than SPA and catheter methods, in both

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hospital and community-based settings.[9] However, contamination rates in CCU are higher than by SPA or catheter collection,[10] ranging from 16 to 38%.[10–14] There is significant heterogeneity in how CCU is obtained in clinical practice:[15] techniques, cleaning solutions, role of collector and cleaning method vary broadly.[14,16] Parents report that obtaining a CCU is time-consuming and messy.[17] One study describes simple measures to improve contamination rates with parents collecting CCU,[15] otherwise there is a paucity of studies analysing technique standardisation for the person collecting the specimen.

Prolonged time spent collecting CCU has potential impacts for both the clinician and patient. Waiting for CCU may tie up valuable resources in clinical settings due to its time-consuming nature, increasing patient length of stay in the emergency department (ED). As time passes, the likelihood of contamination may increase due to difficulty preventing accidental contamination of the peri-genital area or collection jar, or CCU being abandoned by the parent or clinician. There is a lack of evidence to describe how long it takes to collect CCU in pre-continent children in the clinical environment, or whether increased time to obtaining CCU correlates with increased contamination rates. A number of novel techniques have been suggested to speed urine collection in an attempt to address these concerns.[18–22]

The aim of this study was to evaluate the success and time taken for urine collection by CCU, and to investigate if there is a relationship between the time taken to collection and contamination rates. We plan to characterise the diagnostic yield of CCU in diagnosing or excluding UTI by culture in the paediatric ED setting.

Methods

Study design, participants and setting

This prospective observational study was performed at the Royal Children's Hospital (RCH) Melbourne ED. RCH is a large tertiary paediatric hospital in Australia with 82 000 ED presentations per year. Recruitment was conducted between July and November 2014. The RCH Hospital Ethics committee approved the study (HREC 34085D).

Pre-continent children aged between 2 and 48 months, where the treating clinician determined a urine specimen was required, were prospectively recruited following informed verbal consent in a convenience sample. Standardized packs were available at the two main ED staff bases, containing sterile water, gauze, urine jar, timer, consent and data collection forms. ED clinicians were provided with education about the study at staff meetings, clinical handovers and via posters in the ED. A total of 93 nurses and doctors recruited participants for the study. CCU was performed as per RCH clinical guidelines,[23] with initial cleaning of the peri-genital area with sterile water and the parent or carer provided with a sterile container to catch a urine sample. Children able to void on request, or who required an immediate urine sample via another method, were excluded. Data were collected on demographic information, related clinical parameters, clinical indication (see Table 1), outcome of collection attempts and the time taken for collection attempts and voiding. If data recording was incomplete, investigators approached the treating clinicians for clarification or searched medical records for relevant clinical details where possible.

Table 1 Clinician indication for obtaining clean catch urine

Indication	*n* (%)
Fever without focus	127 (59)
Vomiting	31 (14)
Clinically suspected urinary tract infection	28 (13)
Other	9 (4)
Failure to thrive	6 (3)
Irritability	6 (3)
Oedema/Proteinuria	3 (1)
Reduced oral intake	3 (1)
Not specified	3 (1)
Jaundice	1 (0.5)

Urine culture outcomes were determined from hospital laboratory data once results were available. Data from the case record form were entered into Excel (Microsoft 2011) and verified by a second investigator before analyses using STATA, version 14.0 (StataCorp LP, College Station, TX, USA). The study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines for observational studies.[24]

Definitions

The doctor or nurse started the timer when they removed the nappy at the bedside, before commencing cleaning of the peri-genital area. The timer was stopped with any of the following outcomes: (i) 'successful catch' = child voided and urine collected in specimen jar. (ii) 'Missed catch' = child voided but urine was not collected in specimen jar. (iii) 'Stopped' = the CCU collection attempt was ceased for any other reason (e.g. change in clinician preference for collection method, urine sample no longer required or attempt was abandoned for other reasons). The time taken for CCU and outcome was recorded for each attempt per child, if more than one attempt occurred in the ED.

Urine culture results were defined according to hospital laboratory microbiology guidelines for CCU using a 10 μL loop on horse blood agar. Contamination was defined by a urine culture reported as 'mixed growth', if there were ≥2 colony types with colony forming units (CFU) ≥10 000/mL, or ≥3 colony types with CFU ≥ 1000/mL, or where the predominant organism was a known contaminant (e.g. skin or vaginal flora). UTI was diagnosed when a single uropathogen with CFU ≥ 100 000/mL was present, a level comparable to other guidelines.[6] Urine culture with intermediate CFU growth less than these cut-offs were designated as 'no significant growth', with repeat collection recommended if clinically indicated.

Analysis

The sample size was based on the estimated proportion of children voiding within 5 min of initiation of the CCU attempt. This was regarded as the most important value to determine, as it would be the basis for future interventional studies.[21,22,25]

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The voiding rate was estimated at 10% with a variation of 5% around the actual value. This required a sample size of approximately 200 patients.

Comparative analysis was conducted for results of the proportion of voids within 5 min, and first attempt of CCU collection for each child (time spent collecting, outcome and contamination status). Time spent collecting was summarised by median, and interquartile range (IQR) as its distribution was skewed. Outcome and contamination status were summarised by percentages with 95% confidence intervals (CI). Chi-square test was used to compare proportions between groups.

Results

During the study period, 245 participants were enrolled. Twenty-seven were subsequently excluded (17 did not record primary outcome, 7 were outside of age limits, 3 had no identifying information on study form, 1 outlier with collection duration of 540 min) leaving 217 eligible for study inclusion and analysis (see Fig. 1). Eighty-six participants (40%) were female, median age was 10 months (IQR 6–18 months). Specimens were obtained mainly for work-up of fever without focus or other clinical findings predominantly attributable to UTI (Table 1). Twelve percent of participants had a past history of UTI.

In total, there were 247 CCU collection attempts from 217 children, 28 children had two separate collection attempts and 2 children had three attempts during their ED presentation. Of the 217 children, 160 (74%) ultimately had successful CCU collection, 22 (10%) had urine subsequently collected by an invasive method, 31 (14%) had urine collection abandoned and 4 (2%) continued attempted CCU at home. From the 160 CCU specimens obtained, 129 had urine culture performed of which 50 were contaminated (39%). Ten children (8%) had a positive urine culture result of a single pathogen suggesting a diagnosis of UTI.

For the first CCU attempt, the median time spent collecting urine was 30.5 min (IQR 11–66). The median time taken when CCU was 'stopped' was 71 min (IQR 42.5–93), compared with when 'successful' 25 min (IQR 7–46.5) or 'missed' 27 min (IQR 11.6–59). The outcome of the first CCU attempt was 'successful' in 64% (95% CI 58–70%), 'missed' in 16% (95% CI 11–20%) and 'stopped' in 20% (95% CI 15–26%). The likelihood of obtaining successful urine collection decreased after 1 h of

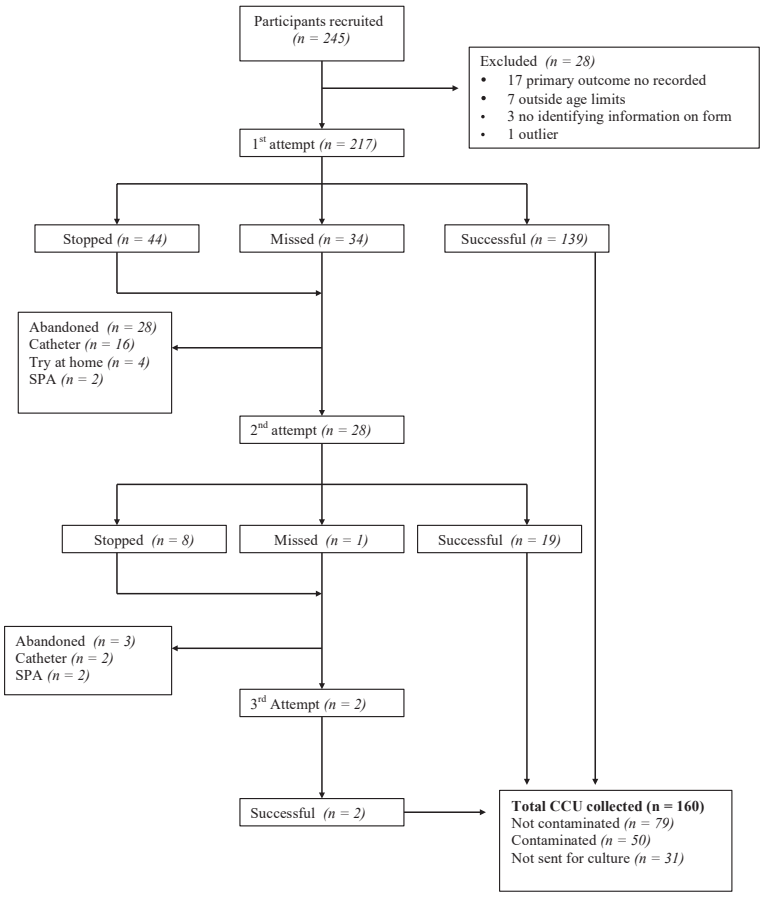


Fig. 1 Outcomes of all urine clean catch attempts. CCU, clean catch urine; SPA, suprapubic aspiration.

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attempted CCU (see Fig. 2). Twenty-seven of 217 children (12%, 95% CI 8–18%) passed urine within 5 min at first CCU attempt. In the younger age group, our study found 16 of 114 infants aged 2–12 months (14%, 95% CI 8–22%) passed urine within 5 min.

There was no difference in contamination by time to successful urine collection. Figure 3 shows that the proportion of contamination by interval of time to successful urine collection does not vary significantly, and CI of proportions overlap.

Females had a higher proportion of contaminated CCU than males, 53% versus 32% ($P = 0.02$) (Table 2). Contamination was highest in the youngest age group (2–6 months). Further analyses of time of last feed and combined collecting time where there were multiple attempts were not statistically significant for contamination.

Discussion

This study prospectively assessed the time taken and success of attempted CCU collection in pre-continent children. The indication for the majority of specimens was investigation of fever without focus, symptoms attributable to UTI or clinical suspicion of UTI. Our findings indicate that CCU attempts can be time-consuming, and only 12% voided within 5 min. Sixty-four percent of first CCU attempts were successful, and as time passes beyond an hour, the likelihood of successfully obtaining CCU plateaued. Three-quarters of patients who voided for successful CCU did so within 46 min, and the median time was similar for 'successful' (25 min) and 'missed' (27 min) CCU attempts.

Clinicians will need to consider these results when they plan to collect a CCU sample. They challenge the role of CCU as the collection method of choice for the investigation of suspected UTI in young children due to the time required, and the proportion of missed and unsuccessful attempts requiring re-collection. These findings suggest that in practice, CCU attempts should be time limited and alternate collection methods considered beyond 1 h. The rate of spontaneous void at 5 min will provide an important baseline value and starting point for sample size calculation for studies attempting to speed CCU in young children.

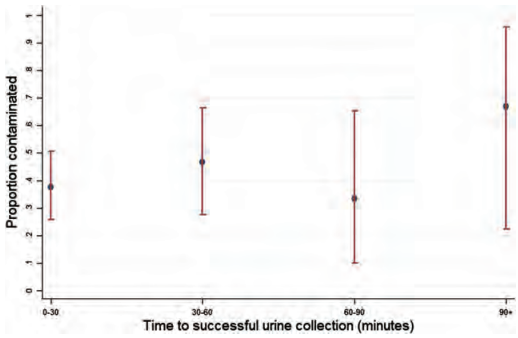


Fig. 3 Proportion of first catch contamination by time to successful urine collection. (●), Proportion contaminated; (⊢), 95% confidence interval.

When culture was performed, a high proportion (39%) were contaminated. There was a significantly higher contamination rate in females, and a trend towards higher contamination in younger infants (2–6 months). In this cohort of patients, the overall proportion of successfully collected, uncontaminated urine culture obtained from a CCU was 79 of 217 (36%), although not all specimens collected were cultured.

When embarking on attempted CCU, we estimate that if all urine specimens successfully collected (160 of 217, 74%) were sent for culture, with a contamination rate of 39% (uncontaminated specimen rate of 61%), a clinician could expect a 45% chance of obtaining an uncontaminated specimen from this method (74% × 61% = 45%).

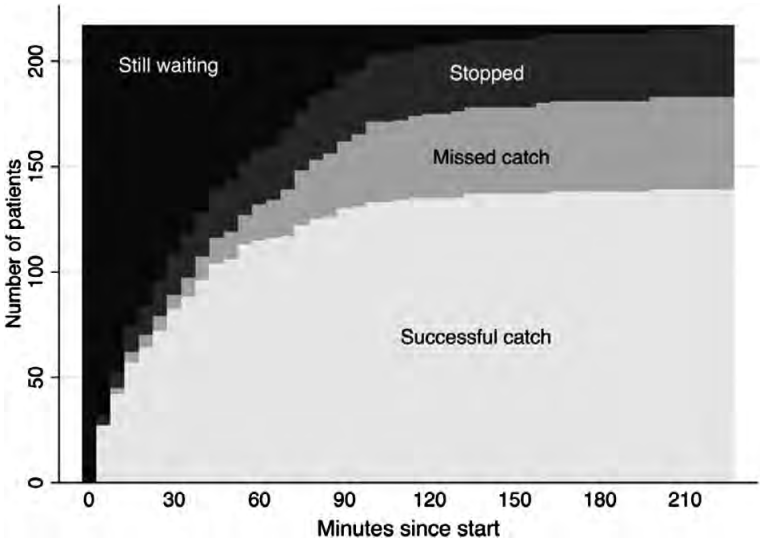


Fig. 2 Distribution of time to successful clean catch urine collection.

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Table 2 Proportion of total clean catch urine (CCU) contaminated, by gender and age group

Variable	Total CCU, *n*	Contaminated, *n*	% contaminated (95% CI)	*P* value
Sex				0.02
Female	47	25	53 (39–67)	
Male	63	20	32 (20–43)	
Difference	—	—	21 (3–40)	
Age group (months)				0.10
2–6	37	21	57 (41–73)	
6–12	39	14	36 (21–51)	
12–24	22	6	27 (9–46)	
>24	12	4	33 (7–60)	

—, No values; CI, confidence interval.

This study found no clear relationship between the time taken for collection and CCU contamination. Our hypothesis that contamination is related to time taken for collection arose from clinical observations that accidental contact of the specimen jar with the peri-genital area after cleaning was common. Furthermore, we hypothesised that such contact was more likely to occur with the passage of time. An explanation for these findings may be that the contamination occurs from commensal organisms present at the distal urethra, with the contact of urine passing the vulva, vagina or labia in girls; or prepuce in boys. This explanation is supported by the ballooning of the prepuce and vaginal reflux seen in a proportion of children (38% boys and 14.3% of girls) during voiding on fluoroscopic micturating cystourethrograms.[26] The recommended collection approach in adults, is that the first void is discarded before obtaining a 'mid-stream' collection. Considering the difficulties obtaining CCU in young children, a definite 'mid-stream' specimen is generally difficult to achieve. Studies on reducing contamination rates in CCU by cleaning are mixed, with some showing external cleaning does not have a significant impact on contamination rates[27,28] whilst a recent systematic review suggests that if non-invasive urine collection is being considered for young children, mid-stream collection with cleansing is recommended.[29]

There is no consensus definition of contamination for CCU culture in children. In published studies where a definition is outlined, numbers of organisms and CFU cut-offs vary.[12,14,17,19,29,30] The definition used in this study was determined by the hospital microbiology laboratory, which stratifies interpretation of culture growth and contamination depending on method of collection, number of organisms and CFU, similar to recommended UK standards for microbiology investigations.[31] The contamination rate found in this study is comparable with rates reported in other studies of CCU.[10–14] Interpretation of microbiological culture results with growth at lower CFU should be interpreted in the clinical context, the presence or absence of pyuria, and squamous epithelial cells on microscopy, and may represent early UTI, contamination or asymptomatic bacteriuria.

This study has some limitations. It relied on opportunistic recruiting by ED clinicians rather than consecutive recruitment, and was conducted in a single tertiary paediatric ED setting. A proportion (19%) of successfully caught urine specimens collected was not sent for laboratory culture and therefore contamination of these specimens could not be determined. This may be due to the urine dipstick results being deemed sufficient for clinical decision-making, despite urine culture being the recommended test for diagnosing UTI in young children.[4–6] We did not measure the preparation time taken prior to commencement of attempt (e.g. whilst encouraging oral intake), or time between attempts when more than one attempt was required. As the clinician was responsible for starting the timer as well as commencing cleaning, a small degree of uncertainty of the measurement is possible. Whilst the majority of specimens were obtained to investigate for UTI, the clinical course may have changed due to interventions (e.g. fluids, treatment, other investigations, observation), changing the clinician's ongoing decision regarding urine collection. Clinicians were aware of the contamination outcomes being recorded and this may have influenced cleaning behaviour, however, contamination rates are similar to previous reports from this ED.[10]

An ideal method of reducing contamination rates and obtaining CCU in a timely manner remains elusive. There is promising evidence for stimulation methods that hasten CCU collection, defining successful collection as a sample obtained within 5 min.[19,20,32] However two of these studies are limited to the Neonatal Intensive Care setting, samples were mostly obtained for reasons other than fever or suspected UTI, and patients with poor feeding and dehydration were excluded, limiting the generalisability of these findings.[19,20]

Excessive time waiting for CCU may have a negative impact on families and clinical resources, particularly where CCU collection is ultimately unsuccessful and subsequent progression to invasive collection methods is required. Fourteen percent of urine collection attempts were abandoned entirely, presumably due to identification of an alternate focus or improved clinical state in the period of time waiting for CCU. The clinician should be aware of the expected contamination rate of CCU, and consider this when selecting the method of urine collection.

Conclusions

This study provides an important perspective for clinicians to consider when considering how to collect a urine specimen from young children, and highlights several limitations of the CCU method. CCU attempts are time-consuming, and have a low rate of diagnostic success for the investigation of UTI with high rates of missed catches and contamination. Our data would suggest that waiting for a CCU beyond an hour is unlikely to be successful: at this time point, the ED clinician might well choose to change collection strategy.

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11.2 PILOT STUDY SUPPLEMENTARY DOCUMENTS

11.2.1 Participant information sheet

HREC Project Number: 34085A

Research Project Title: Urine Clean Catch Urine Collection in the Emergency Department

Principal Researcher: Dr Jonathan Kaufman, Paediatric Registrar, Emergency Department

Version Number: 3 **Version Date:** 08/09/2014

Dear Parent,

Thank you for considering participating in the U3C in ED study. We are hoping to improve the ways we obtain urine samples from young children aged 2 – 24 months who are not yet toilet trained.

Your treating doctor has asked you to collect a urine specimen by the 'clean catch' method. We would like to see if a simple technique may trigger a reflex passing of urine, reducing the time you spend waiting for a sample.

For you and your child, this will involve an additional step:

- **Gently rubbing the skin on the abdomen with a wet piece of gauze, for up to 5 minutes**

The wet gauze may cause very short term discomfort to your child, but may reduce the overall discomfort of waiting a long time trying to catch a sample. Collecting samples faster may also help to reduce the number of samples that are contaminated by germs from the skin, which we will check.

Participation in a research project is voluntary. It is your choice to let your child take part in this research. You do not have to agree if you do not want to. Whatever your decision, it will not affect any treatment or care your child gets, or your family's relationship with The Royal Children's Hospital. If you decide not to participate your doctor will still collect a urine specimen. The results of this research could help benefit other similarly unwell children in the future.

If you or your nurse/doctor decide to stop trying to catch a sample or withdraw from the study, you can do this at any time.

Any information recorded will be stored in a secure area, and is only accessible to staff looking after your child and researchers directly involved with this study. The combined results of the whole study may be published in a medical journal, but without any information that could directly identify your child.

We will record if you have agreed to participate in this study (verbal consent). If you have any questions about the study, please ask the nurse or doctor who is looking after your child.

Yours sincerely

Dr Jonathan Kaufman
Emergency Deparment Registrar
Royal Children's Hospital

If you have any concerns and/or complaints about the project, the way it is being conducted or your child's rights as a research participant, and would like to speak to someone independent of the project, please contact:

Director, Research Ethics & Governance, The Royal Children's Hospital Melbourne on telephone: (03) 9345 5044.

11.2.2 Case record form

U3C in ED: Urine Clean Catch Urine Collection in the Emergency Department
HREC Project Number 34085A Data Collection Form Version 3.3 (24/07/14)

Patient Details (or affix label here)

Surname Given Name Date: _____

Date of Birth / / UR Number Time: _____

Sex ○ Male ○ Female

Consent (from person obtaining verbal consent from parent/carer)

Has the parent/carer been offered the study information sheet? ☐ Yes ☐ No

Have they given verbal consent to participate in this study? ☐ Yes ☐ No

Name and signature of person obtaining consent _____

Clinical Details (all pre-continent children age 2 months - 24 months are eligible)

Is the child continent of urine? ☐ Yes ☐ No ☐ Partially

Is there a past history of UTI? ☐ Yes ☐ No ☐ Unknown

Is there a known urogenital tract abnormality? ☐ Yes ☐ No ☐ Unknown

Indication for obtaining urine specimen:

☐ Fever of unknown origin ☐ Clinically suspected UTI ☐ Metabolic

☐ Other _____ (please state)

Collection Details

Remove nappy, clean genital area, start timer.

Use saline soaked gauze to stimulate the suprapubic area with circular motions for up to 5 minutes.

Time taken to pass urine _____ mins _____ seconds ☐ Did not pass urine <5 mins

If yes, outcome: ☐ Successful catch ☐ Missed catch

If no, plan: ☐ Continue catch attempt ☐ Catheter ☐ SPA

☐ Collection attempt ceased ☐ Other _____

Who was the person catching the urine?

☐ Mother ☐ Father ☐ Nurse ☐ Doctor ☐ Other _____

Satisfaction with technique (please ask parent and circle)

PARENT: (1) Very satisfied (2) Satisfied (3) Neutral (4) Unsatisfied (5) Very Unsatisfied

CLINICIAN: (1) Very satisfied (2) Satisfied (3) Neutral (4) Unsatisfied (5) Very Unsatisfied

PTO

Your Details

Name _____ Position _____

Email _____

Other Comments

Office Record (you do not need to complete this section)

Dipstick leucs

Dipstick nitrites

Micro WBC

Micro RBC

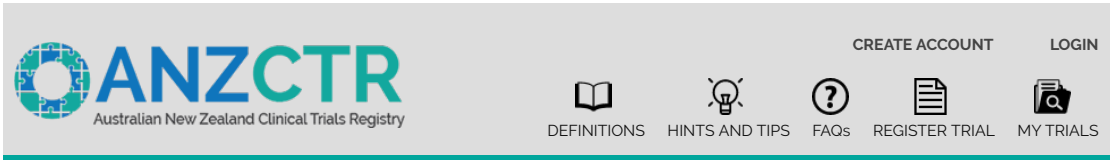
Micro bacteria

Culture

PTO

11.3 RCT SUPPLEMENTARY DOCUMENTS

11.3.1 Trial registration



Trial Review

Please note that ANZCTR will be unattended from Friday 16th December 2016 until Tuesday 3rd January 2017 due to annual University of Sydney closedown.

VIEW TRIAL AT REGISTRATION

VIEW HISTORY

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Trial registered on ANZCTR

Trial ID	ACTRN12615000754549
Ethics application status	Approved
Date submitted	3/06/2015
Date registered	21/07/2015
Type of registration	Prospectively registered

Titles & IDs

Public title	Can gentle cutaneous stimulation with cold fluid soaked gauze hasten Clean Catch Collection of Urine in infants?
Scientific title	Can gentle cutaneous stimulation with cold fluid soaked gauze hasten Clean Catch Collection of Urine in infants, compared to routine genital cleaning alone?
Secondary ID [1]	Nil
Universal Trial Number (UTN)	nil
Trial acronym	Quick-Wee: U3C in ED
Linked study record	

Health condition

Health condition(s) or problem(s) studied:	
Urine sample collection in infants	
Condition category	**Condition code**
Renal and Urogenital	Other renal and urogenital disorders
Public Health	Health service research

Intervention/exposure

Study type	Interventional
Description of intervention(s) / exposure	If randomized to intervention arm, after routine genital cleaning the clinician (or parent/carer with supervision) rubs the suprapubic area of child with cold fluid soaked gauze (normal saline refrigerated at 2.8 degrees celcius) held by disposable plastic forceps in a circular pattern, for up to 5 minutes.
Intervention code [1]	Diagnosis / Prognosis
Comparator / control treatment	Routine cleaning of the genital area before commencing CCU attempt.
Control group	Active

Outcomes

Primary outcome [1]	Primary outcome measure: voiding urine within 5 minutes
Timepoint [1]	Timepoint: binary yes/no outcome at 5 minutes
Secondary outcome [1]	Secondary outcome 1: Parental and clinician satisfaction with the urine collection technique in each group (1-5 satisfaction rating scale)
Timepoint [1]	Timepoint: immediately after urine collection attempt
Secondary outcome [2]	Secondary Outcome 2: If the child voids, whether there is a successful CCU caught, or if the void is missed
Timepoint [2]	Timepoint: immediately after urine collection attempt
Secondary outcome [3]	Secondary outcome 3: Contamination rate of CCU samples obtained within 5 minutes (binary yes/no outcome: urine culture contamination as per hospital laboratory definition)
Timepoint [3]	Timepoint: 48hours after specimen collection
Secondary outcome [4]	We will also collect data relating to patient demographics, reason for presentation/urine collection, and clinical management after CCU attempt from the case record form and hospital records.
Timepoint [4]	Before and 2 days after urine collection attempt

Eligibility

Key inclusion criteria	- Age 1-12 months - Not able to void urine on request - Require and be appropriate for CCU sample collection, as determined by the treating clinician in the Emergency Department
Minimum age	1 Months
Maximum age	12 Months
Gender	Both males and females
Can healthy volunteers participate?	No
Key exclusion criteria	- Children able to void on request to provide urine sample - Children less than 1 month of age - Children greater than 12 months of age - Need for immediate urine sample via sterile method as determined by treating clinician - Anatomical or neurological abnormality affecting voiding or sensation

Study design

Purpose of the study	Diagnosis
Allocation to intervention	Randomised controlled trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	Nursing and/or medical staff will identify potentially suitable patients requiring urine sample collection, and make a decision about the appropriate method of urine sample collection on clinical grounds (independent of this research project), at the point of triage or during clinical assessment. If appropriate for CCU and meeting inclusion criteria, a study researcher or clinician will invite the parents or carer of suitable patients to provide verbal consent to participate in the study. Study participants will be randomly assigned, in a 1:1 ratio, to the intervention (additional suprapubic cutaneous stimulation with cold saline soaked gauze) or standard care, via opaque envelopes containing patient allocation.
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	Study participants will be randomly assigned, in a 1:1 ratio, to the intervention (additional suprapubic cutaneous stimulation with cold saline soaked gauze) or standard care. A statistician not directly involved in the analysis of the study results will prepare the randomisation schedule using random permuted blocks with at least three different block sizes to ensure concealment of allocation. A paper based system using opaque envelopes will be used to allocate participants in the emergency department.
Masking / blinding	Open (masking not used)
Who is / are masked / blinded?	
Intervention assignment	Parallel
Other design features	
Phase	Not Applicable

Type of endpoint(s)	Efficacy

Recruitment

Recruitment status	Completed
Anticipated date of first participant enrolment	1/10/2015
Actual date of first participant enrolment	10/08/2015
Anticipated date last participant enrolled	31/12/2016
Actual date last participant enrolled	15/03/2016
Anticipated date of last data collection	
Actual date of last data collection	17/03/2016
Target sample size	354
Actual sample size	354

Recruitment in Australia	
Recruitment state(s)	VIC
Recruitment hospital [1]	The Royal Childrens Hospital - Parkville
Recruitment postcode(s) [1]	3052 - Parkville

Funding & Sponsors

Funding source category [1]	Charities/Societies/Foundations
Name [1]	Shepherd Foundation
Address [1]	C/ Dr Peter G. Habersberger Suite 33, Cabrini Medical Centre Malvern Victoria 3144, Australia
Country [1]	Australia
Primary sponsor type	Other
Name	Murdoch Childrens Research Institute
Address	Flemington Rd, Parkville 3052 Melbourne, VIC, Australia
Country	Australia
Secondary sponsor category [1]	Hospital
Name [1]	Emergency Department, Royal Children's Hospital
Address [1]	50 Flemington Rd, Parkville 3056
Country [1]	Australia

Ethics approval

Ethics application status	Approved
Ethics committee name [1]	Royal Children's Hospital, Melbourne
Ethics committee address [1]	Flemington Rd, Parkville 3052 Melbourne VIC
Ethics committee country [1]	Australia
Date submitted for ethics approval [1]	
Approval date [1]	29/04/2015
Ethics approval number [1]	35083A

Summary

Brief summary	To determine if suprapubic cutaneous stimulation with cold fluid soaked gauze hastens CCU (within 5 minutes) in children aged 1 – 12 months in the paediatric emergency department, where a urine sample is

	required and the clinician has determined that CCU is an appropriate method of collection.
Trial website	
Trial related presentations / publications	Kaufman J, Fitzpatrick P, Tosif S, et al. The QuickWee trial: protocol for a randomised controlled trial of gentle suprapubic cutaneous stimulation to hasten non-invasive urine collection from infants. BMJ Open 2016;6: e011357. doi:10.1136/bmjopen-2016- 011357 http://bmjopen.bmj.com/content/6/8/e011357.full.pdf
Public notes	

Contacts

Principal investigator	
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Country	Australia
Phone	+613 9345 5522
Fax	
Email	jonathan.kaufman@rch.org.au

Contact person for public queries	
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Country	Australia
Phone	+613 9345 5522
Fax	
Email	jonathan.kaufman@rch.org.au

Contact person for scientific queries	
Name	Dr Jonathan Kaufman
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Country	Australia
Phone	+613 9345 5522
Fax	
Email	jonathan.kaufman@rch.org.au

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11.3.2 Trial funding

SHEPHERD FOUNDATION

Suite 33, Cabrini Medical Centre
MALVERN VIC 3144
Telephone: (03) 9576 0021
Email: pghabers@bigpond.com.au

2nd December 2015

A/Prof Franz Babl
Emergency Department
Royal Children's Hospital
50 Flemington Road
PARKVILLE VIC 3052

Dear A/Prof Franz Babl

RE: Shepherd Foundation Research Grant 2015/16

A Randomised Controlled Trial of the novel Quick-Wee Method

Thank you for grant application to the Shepherd Foundation. Dr Grinzi was most impressed and felt that your research application deserved funding for a period of 12 months.

We would like you to submit an interim report on your project by 30 September 2016 and final report in early 2017.

Could you please provide details as to where the funds are to be forwarded to:

Mr. David Ackland
Chairman, Shepherd Foundation
Lindsay Iles & Co
2nd Floor, 105 Queen Street
Melbourne Vic 3000

50% of your first year grant will be paid at the beginning of January 2016 and a further 50% at the beginning of July 2016.

Congratulations on your successful application.

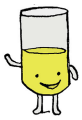
Yours sincerely

Dr Peter G Habersberger
Medical Director, Shepherd Foundation

11.3.3 Participant information sheet

QUICK-WEE STUDY

Catch Urine Quickly, with Quick-Wee



The Royal Children's Hospital Melbourne

Information statement and consent form

HREC Project Number:	35083 A
Research Project Title:	Quick-Wee Study
Principle Researcher:	Dr Jonathan Kaufman, Paediatric Registrar, Emergency Department
Version Number & Date:	V2, 31/07/2015

Dear Parent,

Thank you for considering participating in the Quick-Wee Study. We are hoping to improve the ways we obtain urine samples from young children aged 1 – 12 months who are not yet toilet trained.

Your treating doctor has asked you to collect a urine specimen by the 'clean catch' method. This involves gently cleaning, and then waiting until your child passes urine to catch a sample.

We would like to see if a simple technique may trigger a reflex passing of urine, reducing the time you spend waiting for a sample.

For half of the children in this study, who are allocated at random, this will involve an additional step: Gently rubbing the skin on the abdomen with a piece of gauze soaked with cold water, for up to 5 minutes

The wet gauze may cause very short term discomfort to your child, but may reduce the overall discomfort of waiting a long time trying to catch a sample. Collecting samples faster may also help to reduce the number of samples that are contaminated by germs from the skin, which we will check.

The Children's Excellence in clinical care, research and education

Murdoch Childrens Research Institute

Healthier Kids. Healthier Future.

Information statement and consent form

Participation in a research project is voluntary. It is your choice to let your child take part in this research. You do not have to agree if you do not want to. Whatever your decision, it will not affect any treatment or care your child gets, or your family's relationship with The Royal Children's Hospital. If you decide not to participate your doctor will still collect a urine specimen. The results of this research could help benefit other similarly unwell children in the future.

If you or your nurse/doctor decide to stop trying to catch a sample or withdraw from the study, you can do this at any time.

Any information recorded will be stored in a secure area, and is only accessible to staff looking after your child and researchers directly involved with this study. The combined results of the whole study may be published in a medical journal, but without any information that could directly identify your child.

We will record if you have agreed to participate in this study (verbal consent). If you have any questions about the study, please ask the nurse or doctor who is looking after your child.

Yours sincerely,

Dr Jonathan Kaufman

Emergency Department Registrar, Royal Children's Hospital

Honorary Research Fellow, Murdoch Childrens Research Institute

If you have any concerns and/or complaints about the project, the way it is being conducted or your child's rights as a research participant, and would like to speak to someone independent of the project, please contact:

Director, Research Ethics & Governance, The Royal Children's Hospital Melbourne on telephone: (03) 9345 5044.

11.3.4 Clinician instructions

11.3.4.1 Control arm

QUICK-WEE RCT

STUDY NUMBER _____

YOU HAVE BEEN RANDOMISED FOR: JUST CATCH

00:00



REMOVE NAPPY, START TIMER

00:00 → 00:10



CLEAN PERIGENITAL SKIN (FOR 10 SECONDS)

- using **room-temperature** fluid and dressing pack

00:10 → 05:00



ROUTINE CATCH ATTEMPT (FOR 5 MINS)

- clinician or supervised parent holds specimen jar
- wait for child to void spontaneously
  (no additional stimulation after routine cleaning)
- continue catch attempt for 5 minutes

OUTCOME



Void, catch urine → STOP TIMER: record time

Void, missed catch → Continue to 5mins, then stop

Tried 5mins, no void → Stop at 5mins

Stopped <5mins → Record reason

WHAT NOW?

→ **ASK PARENT**: WERE YOU SATISFIED WITH THIS METHOD OF URINE COLLECTION?
1-5 scale: very satisfied (1) - satisfied (2) - neutral (3) - unsatisfied (4) - very unsatisfied (5)

→ **ASK PARENT**: WOULD YOU TRY THIS METHOD AGAIN? *Yes / No*

→ Please send urine for MC&S if obtained

→ Ongoing clinical management as you decide

→ Fill in the study form: please fill in all questions! Return form and timer.

→ Include your name/email so we can give you a coffee voucher! (if all data completed)

THANK YOU: WEE REALLY APPRECIATE YOUR HELP!

11.3.4.2 Intervention arm

QUICK-WEE RCT



STUDY NUMBER

_____

YOU HAVE BEEN RANDOMISED FOR: COLD-RUB

00:00



REMOVE NAPPY, START TIMER

00:00 → 00:10



CLEAN PERIGENITAL SKIN (FOR 10 SECONDS)

- using **room-temperature** fluid and dressing pack

00:10 → 05:00



COLD RUB: SALINE SOAKED GAUZE (FOR 5 MINS)

- use yellow labelled **cold saline** from Quick-Wee fridge
- **soak gauze piece** from dressing pack
- with plastic forceps, use continuous **circular motions**
- **gently rub** the suprapubic/lower abdomen area
- keep gauze wet: resoak as required
- rub **continuously until void/5mins**

OUTCOME



# Void, catch urine	STOP TIMER: record time
# Void, missed catch	Continue to 5mins, then stop
# Tried 5mins, no void	Stop at 5mins
# Abandoned <5mins	Record reason abandoned

WHAT NOW?

→ **ASK PARENT**: WERE YOU SATISFIED WITH THIS METHOD OF URINE COLLECTION?

1-5 scale: very satisfied (1) - satisfied (2) - neutral (3) - unsatisfied (4) - very unsatisfied (5)

→ **ASK PARENT**: WOULD YOU TRY THIS METHOD AGAIN? *Yes / No*

→ Please send urine for MC&S if obtained

→ Ongoing clinical management as you decide

→ Fill in the study form: please fill in all questions! Return form and timer.

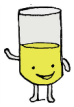
→ Include your name/email so we can give you a coffee voucher! (if all data completed)

THANK YOU: WEE REALLY APPRECIATE YOUR HELP!

Quick-Wee Randomisation Instructions: Cold Rub v1 July 31 2015 JK

11.3.5 Case record form

QUICK-WEE RCT



Catch Urine Quickly, with Quick-Wee

Attach Patient Hospital Sticker Here

Name: _____

DOB: __ __ / __ __ / __ __ __ __

UR: __ __ __ __ __ __ __

Sex: M or F (circle)

START

PART 1: ELIGIBILITY

STUDY SYNOPSIS: Can gentle cold fluid rubbing (Quick-Wee method) trigger voiding for Clean Catch Urine in <5 minutes for infants in the ED

Todays date & time: __ __ / __ __ / __ __ __ __ *(DD/MM/YYYY)* __ __ : __ __ *(24:00)*

Recruited by: _____ **Email:** _____

Are you: (circle) nursing / medical *coffee voucher reward if all CRF data fully completed*

1.1 Inclusion criteria *(tick all that apply) – all 3 required to be eligible*

☐ Aged > 1 month (> 28 days old) and < 12 months (< 365 days old) (corrected age if <36/40)

☐ Not toilet trained (cannot void on request to provide urine sample)

☐ Appropriate for clean catch urine collection

1.2 Exclusion criteria *(tick all that apply) – any exclusion criteria present → excluded*

☐ Require immediate sterile urine sample (<5 minutes)

☐ Anatomical/neurological abnormality affecting voiding/sensation (specify): _____

2.1 Verbal Consent: obtained from parent/guardian? (tick box) ☐ Yes ☐ No

If NO, reason consent not obtained:

☐ Did not want therapy randomly assigned ☐ Did not want cold fluid rubbing intervention

☐ Other (please describe): _____

If eligible for inclusion: **LEAVE NAPPY ON UNTIL RANDOMISATION**

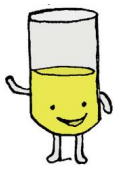
ELIGIBLE: if all inclusion & no exclusion criteria, obtain patient details & informed consent.
Attach patient HOSPITAL STICKER to this form.

NOT ELIGIBLE: if any exclusion criteria or no consent, patient not appropriate for study.
No need to turn over the page. Place form in Quick-Wee research box. And thank you.

DO NOT FILE IN MEDICAL RECORD – FORMS GO IN QUICK-WEE RESEARCH BOX

QUICK-WEE RCT

Catch Urine Quickly, with Quick-Wee



WHAT TO SAY TO PARENTS FOR VERBAL CONSENT

- We need to collect a urine sample from your child, because……
- But collecting urine from young children can be difficult
- We first clean the area to minimise contamination from skin germs
- We then wait to catch a sample when your child wees, but this can take a long time

- We're doing research to try to catch wee samples quicker, with a simple technique
- We gently rub the tummy with a wet, cold piece of gauze, for up to 5 minutes
- In a smaller study, some children weed if we did that, and parents liked the technique

- For this study, 1/2 the children will have just skin cleaning, 1/2 will have the extra rubbing
- It is decided at random which one we do for the first 5 minutes
- After 5 minutes, if they haven't weed, we can decide to keep waiting, or try something else
- Would you be happy to do that?
- **OFFER PARENT INFORMATION SHEET (ATTACHED), OBTAIN VERBAL CONSENT**

COLLECT STUDY MATERIALS, PREPARE FOR CLEAN CATCH

1. Collect Quick-Wee Pack from Study Box (includes all randomisation & urine catch collection materials)
2. Collect yellow-labelled cold saline ampoule from Quick-Wee Fridge (start within 2mins so stays cold)
3. Leave nappy on, prepare materials for clean catch by patient bedside, allocate 'catcher'
4. Have all cleaning materials and sample jar ready, and cold saline (for cold-rub if required)

YOU ARE READY TO RANDOMISE & START INTERVENTION

5. With everything ready by the bedside, nappy still on, open randomisation envelope
6. Remove nappy, start timer (00:00)
7. Clean perigenital skin for 10 seconds (00:00 → 00:10)
8. Intervention: instructions in randomisation envelope (00:10 → 05:00)
9. Stop when urine sample obtained, or timer reads 05:00

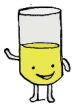
COLD-RUB

or

JUST CATCH

- **IF URINE SAMPLE OBTAINED, PLEASE SEND FOR MC&S**

QUICK-WEE RCT



Catch Urine Quickly, with Quick-Wee

Attach Patient Hospital Sticker Here

Name: _____

DOB: __ __ / __ __ / __ __ __ __

UR: __ __ __ __ __ __ __

Sex: M or F (circle)

PART 2: PATIENT INFORMATION

2.1 Major medical comorbidities? List: _____

2.2 Previous UTI? ☐ Yes ☐ No ☐ Unsure

2.3 Antibiotics in past 48hrs? ☐ Yes ☐ No ☐ Unsure

2.4 Clinician: your assessment of whether child is dehydrated? *(tick one only)*

☐ normal hydration ☐ mild ☐ moderate ☐ severe ☐ unsure

2.5 Clinician: indication to collect a urine sample from this patient? *(tick all that apply)*

☐ specifically suspect a UTI is likely ☐ fever of unknown origin, to exclude UTI

☐ metabolic/electrolyte/jaundice test ☐ unsettled baby

☐ failure to thrive ☐ poor feeding

☐ other, please specify: _____

2.6 What clinical signs are present to suggest possible UTI? *(tick all that apply)*

☐ fever ☐ vomiting

☐ malodorous/discoloured urine ☐ poor feeding

☐ discomfort/pain ☐ unsettled baby

☐ other (please specify): _____

2.7 Clinician: *BEFORE* collecting the urine sample, how likely do you think it is that this patient has a UTI? *(your estimate of probability, mark below on the line)*

(0%) no possibility (50%) certain (100%)

DO NOT FILE IN MEDICAL RECORD – FORMS GO IN QUICK-WEE RESEARCH BOX

QUICK-WEE RCT

STUDY NUMBER _____

Catch Urine Quickly, with Quick-Wee

PART 3: POST-RANDOMISATION RESULTS

3.1 Randomisation details: Randomised to: ☐ COLD-RUB or ☐ JUST CATCH

3.2 Did child void urine <5mins:

☐ Yes: voided at __ minutes __ __ seconds or ☐ No void <5mins

If voided: ☐ Successful catch *(sample obtained)* ☐ Voided but missed catch *(no sample)*

3.3 Who performed each task: *(tick one for each task)*

Standard cleaning: ☐ doctor ☐ nurse ☐ mother ☐ father ☐ other (specify) _____

Cold Rub (if done): ☐ doctor ☐ nurse ☐ mother ☐ father ☐ other (specify) _____

Catching urine: ☐ doctor ☐ nurse ☐ mother ☐ father ☐ other (specify) _____

3.4 Any significant difficulties:

Did you have any significant problems or need to stop before void/5mins: ☐ Yes ☐ No

If any significant problems, please state: _____

If stopped <5mins, please state reason: _____

3.5 If no void/missed catch after 5 minutes, what is your plan now:

☐ Continue clean catch ☐ SPA ☐ Catheter ☐ Abandon collection in ED

☐ N/A: sample obtained ☐ Other (specify): _____

3.6 Parent satisfaction with this urine collection method: (ask parent: 1-5 scale)

☐ very satisfied (1) ☐ satisfied (2) ☐ neutral (3) ☐ unsatisfied (4) ☐ very unsatisfied (5)

** Would you try this technique again? ☐ Yes ☐ No ☐ Unsure

3.7 Clinician satisfaction with this urine collection method: (your thoughts: 1-5 scale)

☐ very satisfied (1) ☐ satisfied (2) ☐ neutral (3) ☐ unsatisfied (4) ☐ very unsatisfied (5)

** Would you try this technique again? ☐ Yes ☐ No ☐ Unsure

* **coffee voucher reward if all questions completed**, forms go into Quick-Wee research box

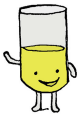
* to contact study team, email us: jonathan.kaufman@rch.org.au

* comments/suggestions: _____

FINISH **THANK YOU: WEE REALLY APPRECIATE YOUR HELP!**

11.4 ECONOMIC EVALUATION SUPPLEMENTARY DOCUMENTS

11.4.1 Clinician survey



Liquid Gold: Health Economic Analysis of Urine Sample Collection

Clinician Survey v1.0 21/11/2017

Introduction:

Thank you for completing this survey as part of our health economic analysis of urine sample collection study.

The study is a health economics cost analysis and modelled decision cost effectiveness analysis of the main methods of urine sample collection used for pre-continent children: non-invasive (bag, clean catch, clean catch with voiding stimulation) and invasive methods (urethral catheterization, suprapubic aspirate).

The population to be evaluated are pre-continent children aged 1-24 months requiring a urine sample in the Emergency Department.

We have constructed a probabilistic decision model, informed by the best estimate of time taken, success rate and contamination rate for each method obtained from a review of the literature.

The researcher will show you the model, explain the structure, and data for time, success and contamination for each arm of the model as obtained from the literature.

- We will ask you for an estimate of critical values based on your local practice. Where published probabilities and data are available from the literature, we will ask you if the current estimates for each data point in the model are considered an acceptable input for a general model.

- Where published probabilities and data are not available from the literature, the data provided by clinicians will be used to inform values for the probabilistic model based on expert opinion.

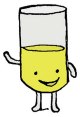
Your responses will be recorded by the researcher in a simple table for estimates where required, and yes or no responses for acceptability of the values of each arm of the model.

Aggregate data will inform values for the model. Identifying details and individual responses will not be reported.

It is estimated this survey will take 10-15 minutes to complete.

If you have any further questions about the study, please contact the Lead Investigator, Dr Jonathan Kaufman, kaufmanj@student.unimelb.edu.au

If you have any concerns and/or complaints about the project, the way it is being conducted or your rights as a research participant, and would like to speak to someone independent of the project, please contact:
Director, Research Ethics & Governance, The Royal Children's Hospital Melbourne on telephone: (03) 9345 5044.



Liquid Gold: Health Economic Analysis of Urine Sample Collection

Clinician Survey v1.0 21/11/2017

Survey & clinician details

RESEARCHER: DATE:

CLINICIAN INITIALS:

SPECIALITY: YEARS CLINICAL EXPERIENCE:

Collecting a sample in ED

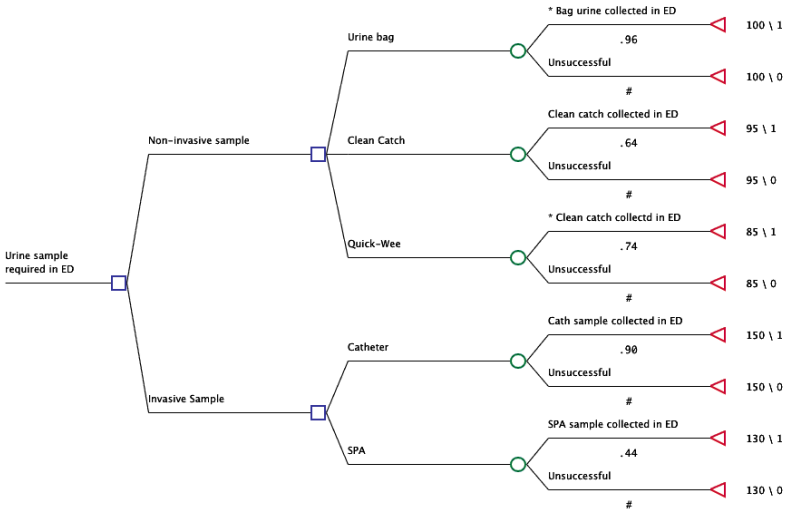
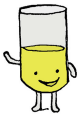


Table 1: Model Inputs: Time & Success/Contamination Probabilities

Parameter	Clinician Estimate	Model Estimate	Model Estimate Source	Acceptable Input (Y/N)
BAG				
Time		85 mins	McKune 1989 [1]	
Success		96%	Alam 2005 [2]	
CLEAN CATCH				
Time		30.5 mins	Tosif 2017 [3]	
Success		64%	Tosif 2017	
QUICK-WEE				
Time		** 5 mins only		
Success		30% < 5mins	Kaufman 2017 [4]	
CATHETER				
Time		12 mins	Baumann 2008 [5]	
Success		90%	Poonai 2015 [6]	
SPA				
Time		not found in literature	n/a	
Success		44%	Munir 2002 [7]	



Collecting a definitive sample

Table 2: Model Inputs: Time & Success/Contamination Probabilities

Parameter	Clinician Estimate	Model Estimate	Model Estimate Source	Acceptable Input (Y/N)
BAG				
Dipstick positive/send culture anyway		72%	Schroeder 2005 [8]	
Contamination		46%	Tosif 2012 [9]	
Patient recalled if culture contaminated	to GP: to ED:	not found in literature	n/a	
CLEAN CATCH				
Dipstick positive/send culture anyway		80%	Tosif 2017 [3]	
Contamination		26%	Tosif 2012 [9]	
Patient recalled if culture contaminated	to GP: to ED:	not found in literature	n/a	
QUICK-WEE				
Dipstick positive/send culture anyway		85%	Kaufman 2017 [4]	
Contamination		27%	Kaufman 2017 [4]	
Patient recalled if culture contaminated	to GP: to ED:	not found in literature	n/a	
CATHETER				
Dipstick positive/send culture anyway		95%	Schroeder 2005 [8]	
Contamination		12%	Tosif 2012 [9]	
Patient recalled if culture contaminated	to GP: to ED:	not found in literature	n/a	
SPA				
Dipstick positive/send culture anyway		100%	RCH CPG 2015 [10]	
Contamination		1%	Tosif 2012 [9]	
Patient recalled if culture contaminated	to GP: to ED:	not found in literature	n/a	

11.5 QUALITATIVE STUDY SUPPLEMENTARY DOCUMENTS

11.5.1 Plain language statement and consent

THE UNIVERSITY OF MELBOURNE

WHAT'S THE CATCH?

Barriers and enablers to collecting urine samples from young pre-continent children in primary care.

PLAIN LANGUAGE STATEMENT

1. Your consent

You are invited to take part in this research project. This Plain Language Statement contains detailed information about the research project. Please read this form and feel free to ask any questions.

2. Who is conducting the research?

This research is being conducted by researchers at the Department of General Practice at the University of Melbourne, involving Professor Meredith Temple-Smith, Associate Professor Lena Sanci and PhD student researcher Dr Jonathan Kaufman.

3. What is the purpose of the research?

The aim of this study is to explore the barriers and enablers to collecting urine samples from young pre-continent children in the General Practice setting.

4. What will I be asked to do?

If you agree to participate, you will be invited to take part in a single interview with a member of the research team. The interview can be done over the phone or in person at your place of work during opening hours and will be audio-recorded so that it can be typed out later for analysis. We estimate that the interview will take about 20-30 minutes. The interview will involve some basic demographic questions and open-ended questions on:

- Preferred methods of collecting urine samples from young children who are not yet toilet trained
- Successfully collecting a sample
- Barriers to collecting a sample

You do not have to answer any questions you are not comfortable answering. With your permission, we may contact you after you have completed the interview if we need further clarification or explanation about the information you have provided.

5. Possible benefits

The results of this study will offer insight into this area of clinical practice, to inform future guideline recommendations and future targeted research. GPs will not be reimbursed for participating in this part of the study.

6. Risks in participating

We do not anticipate any risks will be posed to you in participating in this study. You are under no obligation to answer all questions, and are free to withdraw from the study at any time. Involvement or non-involvement in the study will in no way impair their association with VicReN or The Department of General Practice.

7. How will my confidentiality be protected?

All information used for the purposes of publications or conference presentations will be de-identified and you will either be referred to by a study ID number or pseudonym only.

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The small sample size in this study offers potential for revealing identity so any information obtained that can identify you will be removed from transcripts. It will be disclosed only with your permission, or in compliance with the law. Any identifying data we collect will be stored separately from coded interview data, in a locked drawer or password protected computer database at The Department of General Practice. Data access will be restricted to only those involved in this study. The Department of General Practice requires a staff allocated, authorised swipe pass to enter the buildings after hours and remains locked. Entry during business hours is managed by reception staff.

The information collected as part of this study will be destroyed after five years following the publication of the final report, resource or journal article from the research. Documents will be shredded and electronic recording material will be erased. It is possible for information to be subject to subpoena, freedom of information request or mandated reporting by some professions. However, given the general nature of the information sought in this research, its release as a consequence of these legal processes is extremely unlikely.

8. Do I have to take part?

Participation in this study is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you decide to withdraw from the project we will not use any of the information or data you have provided to us.

9. Results of the study

A journal article and PhD thesis chapter will be produced from this research and the findings presented at relevant conferences. You will be able to receive a summary of the research findings, by contacting either of the researchers listed below or by completing the tick box in the consent form indicating you would like to be emailed a copy of the study results.

10. Ethics

This research project has been approved by the Human Research Ethics Committee of The University of Melbourne. If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact the Manager, Human Research Ethics, Office for Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Fax: +61 3 9347 6739 or Email: HumanEthics-complaints@unimelb.edu.au. All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project (ID number: 1853075.1).

11. Where can I get further information?

If you would like to know more about the research, or if you have any concerns during the course of the research, please email or telephone us using the details below:

Professor Meredith Temple-Smith	M: 0429 858 248	E: m.temple-smith@unimelb.edu.au
Dr Jonathan Kaufman	M: 0411 966 542	E: jkaufman@unimelb.edu.au
Associate Professor Lena Sanci	Ph: 8344 7276	E: l.sanci@unimelb.edu.au

12. How do I agree to participate?

If you are willing to participate in the interview please read and complete the consent form.

THE UNIVERSITY OF MELBOURNE

CONSENT FORM

Principal researcher: Professor Meredith Temple-Smith
Other researchers: Associate Professor Lena Sanci, Dr Jonathan Kaufman (PhD student researcher).

Professor Meredith Temple-Smith	M: 0429 858 248	E: m.temple-smith@unimelb.edu.au
Dr Jonathan Kaufman	M: 0411 966 542	E: jkaufman@unimelb.edu.au
Associate Professor Lena Sanci	Ph: 8344 7276	E: l.sanci@unimelb.edu.au

I have been given a Plain Language Statement about the above named research. I understand this project aims to explore the barriers and enablers to collecting urine samples from young pre-continent children in the General Practice setting.

I understand this form is to gain my consent to participate in this research and I acknowledge:

1. I have read and understand the Plain Language Statement. I consent to participate in the project named above, the particulars of which are to participate in an individual interview which will be audio-taped. A written copy of the information has been given to me to keep.
2. I authorise the researchers to use the information I provide for inclusion in a PhD thesis chapter and any academic journal articles and conference presentations relating to the research referred to above.
3. I have been informed that my participation in this project is voluntary and I am free to withdraw from the project at any time without explanation or prejudice and to withdraw any data previously supplied.
4. I understand the project is for the purposes of research.
5. I understand the small sample size in this study may make me more identifiable however any information obtained in connection with this project, and that can identify me, will remain confidential subject to any legal requirements. I understand I will be referred to either by a study ID number or a pseudonym in any publications or reports arising from this study.
6. I understand all data will be securely stored at The Department of General Practice in locked cabinets or password protected databases and access will be restricted to only those involved in this study.

Please tick these boxes if you consent to us contacting you after the interview for the following reasons (contact will be via email).

☐ I agree to being contacted after I have completed the interview if further clarification is required

☐ I would like to receive a copy of the study results directly.

I, _____ **(your name)**

voluntarily consent to taking part in this research project.

Signature: **Date:**

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11.5.2 Interview schedule

What's The Catch Interview Schedule

What's The Catch Interview Schedule

Pre-amble

I'm Jonathan and I am a paediatrician and PhD student in the Department of General Practice at the University of Melbourne.

I'm part of a team conducting research looking at how we investigate urinary tract infections in young children.

Specifically, I'd like to talk today about young, pre-continent children (e.g <2yo), and collecting urine samples in the GP setting.

I'm interested in your views about the barriers and enablers to collecting these samples.

Our aim is to better understand this process in the GP context, which hasn't previously been researched, so we can target future guidelines and research accordingly.

We can provide you with our findings at the completion of the research project. You can withdraw your participation at any time. Your responses will be de-identified. I will be recording our interview. We can stop the interview and recording at any time.

Section 1: Participant Characteristics

1.1	Age
1.2	Male/female
1.3	Full or part-time (EFT)
1.4	Training level: fellow/registrar
1.5	Country where primary medical/nursing degree obtained
1.6	Years working in General Practice
1.7	Practice location & postcode: inner metropolitan, outer metropolitan, regional, rural
1.8	Number of GP's working at practice (full time equivalent)
1.9	Number of nurses working at practice (full time equivalent)
1.10	Type of clinic: private, corporate, community, super, other
1.11	In an average week, what percentage of your patients are children?
1.12	Do you have a special interest in paediatric patients
1.13	Do you have any postgraduate training in paediatrics (diploma level or above)

Section 2: Methods of urine sample collection from young children in general practice

I'm going to ask a few questions about a clinical scenario. It's not a test, and there are no right or wrong responses. I'm just genuinely interested in your answers.

SCENARIO A: You see a febrile, 6 month old child with fever and vomiting. On examination there is no focus for their fever, and they are not otherwise unwell. The child is still feeding normally. The parents report the urine has a different smell than usual.

2.1 Would you collect a urine sample as part of their care?

2.2 How would you do that in your practice? If not, what would you do?

PROMPTS
2A What method of collection would you use
+ urine bag, clean catch, voiding stimulation, catheter, SPA

2B Why did you choose that method?
+ did you consider any specific guidelines

2C Are there other methods you might use at other times?

2D Is collecting urine from young children something you do often in your practice?
+ daily, weekly, monthly

2E Who is the person who usually does the urine collection in your practice?
+ doctor, practice nurse, parent/family, refer to ED

2F If the parent/family collect the sample, how do you explain the process to them?
+ verbal instructions, how long explaining
+ written instructions, where do you get these from
+ do they do the collection in the practice, or at home

2G Are there any instances where you would refer/seek help?
+ examples?
+ if you could collect a sample quickly, would you still refer them?

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HREC: 1853075.1 **Date:** 10/10/2018 **Version:** 1.0

Section 3: Barriers to sample collection

3 What can make it difficult to collect urine samples from young children?

PROMPTS
3A What are your thoughts on what the barriers are?

3B Can you predict which patients the collection is likely to be challenging for?

3C Do you have equipment for collecting urine samples available in your practice?
+ adhesive urine bag, urine specimen jar, cleaning fluid, gauze, other

3D Would you do a catheter or suprapubic aspirate procedure in your practice?
+ is the equipment available?
+ would you feel confident to perform the procedure?

Section 4: Enablers for sample collection

4 What can make it easier to collect urine samples from young children?

PROMPTS
4A What are your thoughts on what factors can make this successful?

4B Can you predict which patients collection will likely work for?

4C Is there anything you can think of that would make the collection process easier in general?

Section 5: Alternative collection strategies

5 What do you do if the initial collection attempt is unsuccessful?

PROMPTS
+ try again same method
+ try a different method
+ make a clinical decision without a sample
+ observe and review again later
+ refer to ED

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Section 6: Specific collection methods

6 Can you tell me what you think about other collection methods?

PROMPTS
+ urine collection bags
+ clean catch
+ voiding stimulation methods (like lumbar/bladder stimulation or Quick-Wee)
+ catheterisation
+ suprapubic needle aspiration

+ what are the pros and cons of that method
+ do you ever use that method in your practice

Conclusion

Thank you very much for participating in this interview.

Do you have any questions or anything else you'd like to add?

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HREC: 1853075.1 **Date:** 10/10/2018 **Version:** 1.0

11.6 LITERATURE REVIEWS

A separate literature review was performed for each of the three key research areas of this thesis, including:

- voiding stimulation methods
- economic evaluation of urine sample collection methods
- attitudes to clinical practice for urine sample collection

Keywords for each database were derived from example articles initially identified by the doctoral candidate. The doctoral candidate received assistance from RCH Librarian Ms Poh Chua with designing and undertaking the three literature reviews. Databases searched included Medline, Embase and PubMed, accessed via the Royal Children's Hospital OpenAthens portal. The search strategies utilised for each topic and each database are included below.

For each literature review topic, search results from the databases were combined and then duplicates removed using Endnote Version 8 bibliography software. Studies were considered relevant if they related to urine sample collection from pre-continent children and were published in English. Reference lists of included studies were searched for further relevant studies. Automatic monthly search updates were set-up in each database to ensure subsequent relevant publications were noted.

For each literature review topic, a flow chart summarising the search results and study selection is included in the relevant chapter, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines recommended flow-chart. [231] Additional supplementary information from each literature search not included in the preceding chapters is detailed below.

11.6.1 Voiding stimulation methods literature review

The initial search was undertaken in May 2015, and updated in January 2020. Studies were included according to the criteria listed below. 11 relevant studies were identified, as described in section 4.7 of the thesis.

Population:

Pre-continent children who require a urine sample to evaluate potential UTI.

Interventions:

Any non-invasive method used to stimulate urination.

Comparison:

With or without comparison to another intervention or standard care.

Outcomes:

Voiding of urine and/or collection of a urine sample.

Database: Medline
1. Urination/
2. Physical Stimulation/
3. (child* or neonat* or infant* or pediatr* or paediatr*).mp
4. Urinary Tract Infections/di [Diagnosis]
5. specimen handling/ or urine specimen collection/
6. 1 and 2
7. (urine and (collect* or specimen* or sampl* or culture*)).mp
8. 4 and (5 or 7)
9. *specimen handling/ or *urine specimen collection/
10. 6 or 8 or 9
11. 3 and 10
12. limit 10 to (“newborn infant (birth to 1 month)” or “infant (1 to 23 months)” or “preschool child (2 to 5 years)”)
13. 11 or 12

Database: Embase
EMBASE SEARCH 1. urinary tract infections/di [diagnosis] 2. urine sampling/ 3. urinalysis/ or urine culture/ 4. laboratory diagnosis/ or diagnosis/ or laboratory test/ 5. (urine or urinary).tw.kw 6. 4 and 5 7. 1 or 2 or 3 or 6 8. (child* or neonat* or infan* or toddler* or pediatr* or paediatr*).mp. 9. 7 and 8

Database: PubMed
((“Physical Stimulation/instrumentation”[Mesh:noexp] OR “Physical Stimulation/methods”[Mesh:noexp]) AND (“Urination/instrumentation”[Mesh] OR “Urination/physiology”[Mesh])) OR (((((urine) AND (“Specimen Handling/diagnosis”[Mesh] OR “Specimen Handling/diagnostic use”[Mesh] OR “Specimen Handling/methods”[Mesh] OR “Specimen Handling/physiology”[Mesh])) OR (“Urine Specimen Collection/instrumentation”[Mesh] OR “Urine Specimen Collection/methods”[Mesh])) AND (infant[MeSH])) OR ((((urine) AND (“Specimen Handling/diagnosis”[Mesh] OR “Specimen Handling/diagnostic use”[Mesh] OR “Specimen Handling/methods”[Mesh] OR “Specimen Handling/physiology”[Mesh])) OR (“Urine Specimen Collection/instrumentation”[Mesh] OR “Urine Specimen Collection/methods”[Mesh])) AND (child, preschool[MeSH]))))

11.6.2 Economic evaluation literature review

The search was undertaken in May 2017. Studies were included according to the criteria listed below. 4 relevant studies were identified, which are described in section 6.4 of the thesis.

Population:

Pre-continent children who require a urine sample to evaluate potential UTI.

Interventions & Comparison:

Common urine sample collection methods including urine pads, bags, clean catch, urethral catheterisation and suprapubic needle aspiration.

Outcomes:

Cost of urine sample collection.

Database: Medline
1. Urinary Tract Infections/ec [Economics]
2. Urinalysis/
3. Urine/mi [Microbiology]
4. Urine Specimen Collection/
5. specimen collection/
6. (urine or urinary).tw,kf.
7. 5 and 6
8. Urinary Tract Infections/
9. 2 or 3 or 4 or 7 or 8
10. “costs and cost analysis”/ or cost-benefit analysis/ or “cost of illness”/ or health care costs/ or direct service costs/ or hospital costs/ or health expenditures/
11. exp models, economic/
12. Health Resources/ec, ut [Economics, Utilization]
13. markov chains/
14. quality-adjusted life years/
15. 10 or 11 or 12 or 13 or 14
16. 9 and 15
17. 1 or 16
18. limit 17 to “all child (0 to 18 years)”
additional limits: - limit to children

Database: Embase
1. urinary tract infections/di [diagnosis]
2. urine sampling/
3. urinalysis/ or urine culture/
4. laboratory diagnosis/ or diagnosis/ or laboratory test/
5. (urine or urinary).tw.kw
6. 4 and 5
7. 1 or 2 or 3 or 6
8. “healthcare cost”/ or “cost benefit analysis”/ or economic evaluation/ or health economics/ or “cost effectiveness analysis”/ or “cost”
9. economic model/
10. “decision tree”/
11. “hospital cost”/
12. health care utilization/
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. limit 14 to child <unspecified age>
16. from 15 keep 1-168

Database: PubMed
(urine OR urinary OR UTI OR urinalysis) AND (economic* OR cost OR costs OR costing* OR cost-benefit OR “cost benefit” OR markov OR utilization OR utilization OR expenditure) AND (newborn* OR neonat* OR infan* OR pre-schooler* OR preschooler* OR child OR children OR childhood OR adolescen* OR pediatric* OR paediatric* OR youth* OR teen OR teens OR teenage*) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint)

11.6.3 Qualitative analysis literature review

The search was undertaken in November 2017. This was a two part search as listed below. Studies were included according to criteria below. 27 relevant studies were identified, with the overall findings summarised in section 7.4 of the thesis, and with a further table summarising each study included below.

Population:

Pre-continent children who require a urine sample to evaluate potential UTI.

Interventions & Comparisons:

Common urine sample collection methods including urine pads, bags, clean catch, urethral catheterisation and suprapubic needle aspiration.

Outcomes:

Clinician's attitudes, practice patterns and guideline adherence and studies involving surveys, questionnaires and qualitative research with clinicians.

PART 1 SEARCH TERMS: QUALITATIVE RESEARCH

Database: Medline
1. Urinary Tract Infections/di [Diagnosis]
2. specimen handling/ or urine specimen collection/
3. (urine and (collect* or specimen* or sampl* or culture*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. exp qualitative research/
5. (11 or 12 or 13) and 14

Database: Embase
1. urinary tract infection/
2. urine sampling/
3. urinalysis/ or urine culture/
4. laboratory diagnosis/ or diagnosis/ or laboratory test/
5. (urine or urinary).tw,kw.

6. 4 and 5

7. exp qualitative research/

8. (qualitative adj (research or study)).tw,kw.

9. (1 or 2 or 3 or 6) and (7 or 8)

PART 2 SEARCH TERMS: ATTITUDES, PRACTICE PATTERNS, GUIDELINE ADHERENCE, SURVEYS, QUESTIONAIRRES

Database: Medline
1. (child* or neonat* or infan* or toddler* or pediatr* or paediatr*).mp
2. Urinary Tract Infections/di [Diagnosis]
3. specimen handling/ or urine specimen collection/
4. (urine and (collect* or specimen* or sampl* or culture*)).mp
5. “attitude of health personnel”/ or attitude to health/ or health knowledge, attitudes, practice/
6. Practice Patterns, Physicians’/
7. Guideline Adherence/
8. “surveys and questionnaires”/ or exp health care surveys/
9. Medical Audit/
10. (2 or 3 or 4) and (5 or 6 or 7 or 8 or 9) and 1

Database: Embase
1. urinary tract infection/di [Diagnosis]
2. urine sampling/
3. urinalysis/ or urine culture/
4. laboratory diagnosis/ or diagnosis/ or laboratory test/
5. (urine or urinary).tw,kw.
6. 4 and 5
7. exp health personnel attitude/
8. attitude to health/
9. clinical practice/
10. protocol compliance/
11. health survey/
12. questionnaire/ or open ended questionnaire/ or structured questionnaire/
13. clinical audit/
14. (child* or neonat* or infan* or toddler* or pediatr* or paediatr*).mp.
15. (1 or 2 or 3 or 6) and (7 or 8 or 9 or 10 or 11 or 12 or 13) and 14
16. (*urinary tract infection/di or *urine sampling/ or (*urinalysis/ or *urine culture/) or 6) and (exp *health personnel attitude/ or *attitude to health/ or 9 or 10 or 11 or 12 or 13) and 14

Database: PubMed
((urine AND (collect* OR specimen* OR sampl* OR culture*)) OR “urinary tract” OR UTI) AND (knowledge OR attitude* OR “clinical practice” OR “physician practice” OR guideline OR survey OR surveys OR questionnaire OR questionnaires OR audit OR qualitative) AND (newborn* OR neonat* OR infan* OR toddler* OR child OR children OR childhood OR pediatric* OR paediatric*) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint)

Table 15: Qualitative studies full evidence summary

PRIMARY CARE GENERAL PRACTICE				
Study	**Study Type & Aims**	**Participants & Setting**	**Results**	**Summary**
Dighe, 1984, General practice management of childhood urinary tract infection. [278]	Questionnaire to assess incidence of childhood UTI in primary care, and probe attitudes to investigations considered necessary in first time childhood UTI.	60/100 GPs (60% response rate) and 17/20 paediatricians (80% response rate) South East Thames Region, UK	Found significant inconsistencies in the management plans from both GPs and paediatricians. Of 57 consultations in which UTI was diagnosed, only 9 cases were confirmed with urine culture (16%).	Study did not relate to urine sample collection method specifically. Showed significant variation in other aspects of clinical practice for UTI management. Many UTIs were diagnosed without subsequent urine culture confirmation.
Harmsen, 2009, How do Dutch general practitioners diagnose children's urinary tract infections? [279]	Retrospective chart review. To study which tests general practitioners used to diagnose UTI in children.	148 children, 0-12yo, diagnosed with UTI by their GP. 49 Dutch general practices	97% had at least a dipstick test. The percentage of children with urine culture was low (37%), despite the recommendation to culture all urines.	Many children were diagnosed with UTI without subsequent culture confirmation. Did not report specific collection method used.

Jadresic, 1993, Investigation of urinary tract infection in childhood. [280]	Questionnaire survey of GPs. Assessed attitudes of GPs towards assessment and management of paediatric UTIs.	182 GP's in a UK district (Gloucester). 93% response rate (182/195).	6/182 (3%) would treat UTI on weekdays with no urine sample. 94/182 (52%) would treat UTI on weekends with no urine sample, likely due to practical difficulties.	Authors conclude that the practical difficulties faced by GPs when investigating and managing children with UTI must be resolved. Specific difficulties not further explored.
Kennedy, 2010, A survey of the management of urinary tract infection in children in primary care and comparison with the NICE guidelines [126]	Postal survey Aimed to establish current practices for UTI diagnosis and management amongst GPs, compared to recently published guidelines.	All (69) general practices in a single health region in Ireland (County Mayo 50 (72%) GPs completed the questionnaire.	For collecting urine samples from a one year old child, 80% of GPs recommended urine bags, and the remaining 20% recommended clean catch sample collection.	Study showed a clear preference by GPs for the use of urine collection bags.
Platt, 2015, Implementation of NICE guidance on urinary tract infections in children in primary and secondary care [193]	Retrospective multisite audit of compliance with the 2007 NICE paediatric UTI guidelines across primary and secondary care services in England.	10 general practices, 3 paediatric units, 2 paediatric EDs and 2 general EDs. 1149 children were audited (682 from primary care, 467 from secondary care).	Criteria 1: All children under 3 years of age presenting with unexplained fever ≥38°C should have a urine sample tested within 24 h Compliance with criteria 1 was 28% overall, 22% in GP, 36% in ED and 51% in paediatric units.	Concluded that urine testing for UTI was not being considered in many children under three with unexplained fever. Authors suggest results indicate significant shortcomings in the implementation of NICE UTI guidance.

Montini, 2015, The challenges of implementing the 2007 UK guidelines for paediatric urinary tract infection [281]	Editorial for the above Platt article		Editorial states regarding the NICE UTI guideline that "there is a gap between the ideals of the academics that formulate them and real world application by primary care physicians". and "the gap relates to major time constraints and the large number of paediatric and adult patients that attend primary care practices."	Editorial states "Guidelines have also been developed for all manner of illnesses, subjecting general practitioners to information overload." Conclude that the NICE UTI guidelines are too complex, and that clear and concise guidelines are required for GPs.
van der Voort, 1997, The struggle to diagnose UTI in children under two in primary care [282]	Questionnaire via medical journal, including quantitative and qualitative items. Aimed to assess management of febrile children and UTI in children <2yo amongst GPs, and identify some reasons for the difficulties diagnosing UTIs.	82 GPs responded. UK and Ireland.	Approximately 50% use bag collection, 25% clean catch, 25% do not collect urine samples at all in their practice. Urine collection was often done at home by parents, and 6% sent the child to hospital for urine collection. 15% reported practical issues regarding urine sample collection, e.g: "how do you expect mums with five children in a council flat to cope when a clean catch fails in hospital with trained nurses available 24 hours a day"	1 in 4 were unable to exclude UTI due to general difficulty obtaining a urine sample. A range of obstacles were identified: time constraints, parental co-operation, availability of equipment (especially after hours). Authors state: "The techniques for collecting urine samples and testing for UTI require improvement".

Vernon, 1997, How general practitioners manage children with urinary tract infection: an audit in the former Northern Region [146]	Postal questionnaire: how GPs manage children with suspected UTI, and their perception of their training needs.	Random sample of 494 GPs in the former Northern Region, UK (26% of all GP's in the region) 333 (67.4%) GPs replied.	Some GPs always collect and test urine samples. Some never collect urine samples and just treat blindly. In the open responses, the practical difficulties in collecting urine from children were a common theme.	GP's often diagnose and treat UTI without obtaining a urine sample. Practical difficulties obtaining a sample were a common theme.
PAEDIATRICS				
Study	**Study Type & Aims**	**Participants & Setting**	**Results**	**Summary**
Bhojani, 2010, Compliance with NICE guidelines for urinary tract infections: a survey among the paediatric trainees of the London Deanery [283]	Online Survey. Aimed to assess the awareness and compliance of paediatric trainees with the revised 2007 NICE UTI Guidelines.	190 paediatric trainees at the London Deanery, UK. Response rate 20% (190/930).	94% were aware of the guidelines, but only 74% used them routinely. 80% used clean catch as their primary method of urine collection, 20% used urine bags.	Most trainees were aware of the guidelines, and followed guideline recommended methods for collecting urine samples.
Bunting-Early, 2017, The Need for Improved Detection of Urinary Tract Infections in Young Children [284]	Online quantitative survey developed from qualitative interviews. Aimed to explore possible barriers to diagnosing febrile UTI's in very young children.	218 community pediatricians in Pennsylvania, US. Response rate 10% (218/2183).	If clean catch urine was not possible, 81% would collect by catheter, 16% urine bag, and 3% would send the child to ED. 60% believed that delays in the detection of febrile UTI's were common. Only 54% were comfortable performing catheterisation.	Paediatricians believed that delays in UTI diagnosis are common, and not all were comfortable performing catheterisation. Authors state "(findings) underscore a desire and need for innovative screening methods and less invasive testing".

Copp, 2013, Use of urine testing in outpatients treated for urinary tract infection [124]	Retrospective analysis from a large claims database. Characterised urine tests used in antibiotic treated paediatric UTI episodes.	Children <18yo with outpatient diagnosed paediatric UTI. 40,603 UTI episodes, 2002-2007 from the Innovus i3 database, US.	Of 40,603 treated UTI episodes in 28,678 children, urinalysis was performed in 76%, and urine culture in 57%. Of children <2 years, 32% had no urinalysis or culture performed for an antibiotic-treated UTI episode.	Urine sample tests were not performed for a substantial percentage of antibiotic treated paediatric UTIs.
Coutinho, 2014, Pediatrician non-compliance with the American Academy of Pediatrics guidelines for the workup of UTI in infants [125]	Email survey. Assessed urine collection preferences and adherence to the AAP UTI guidelines.	US paediatricians from the New Jersey Chapter of American Association of Pediatrics. 10% response rate (160/1650).	46% preferred sample collection by catheterisation, 35% varied the method depending on the specific clinical scenario. 13-18% of clinicians preferred urine bag collection for culture, against recommended methods.	Catheterisation was the preferred method of urine sample collection by US paediatricians. Some clinicians preferred urine bag samples, against AAP guideline recommendation.
Hadjipanayis, 2015, Current primary care management of children aged 1-36 months with urinary tract infections in Europe: large scale survey of paediatric practice [134]	Web based survey. Described practice of European paediatricians for diagnosis and management of UTI in children aged 1–36 months, and compared practice with guidelines.	1129 paediatricians (1129/1601, 71% response rate) Primary and secondary care paediatric practices in 26 European countries	Urine bags were the preferred method of sample collection (53% for infants <3 months, 59% for children 4–36 months of age) There were significant differences in preferences between countries.	Heterogeneity in practice among European countries was noted, with discrepancies between guidelines and actual practice regarding the diagnosis and management of urinary tract infections in young children.

Newman, 2002, Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study [196]	Prospective cohort study. Aimed to determine predictors and results of urine testing of young febrile infants in outpatient settings.	573 pediatricians from 219 US practices. 3066 febrile infants <3 months of age.	54% had their urine tested, 10% had a UTI. Of urine samples sent for culture, 70% were collected by catheterisation, 25% by urine bag, 3% by SPA, and 2% by clean catch.	US pediatricians favour catheterisation to collect urine samples, but a quarter use urine bags.
Roberts, 2002, Urinary tract infections in young febrile infants: is selective testing acceptable? [285]	Editorial for the above Newman article.		Editorial states: "Do practitioners follow published guidelines, referring specifically to routine urine testing for UTI in the evaluation of febrile infants? Of the 3066 infants enrolled in the PROS Febrile Infant Study, only 1775 had their urine tested. Therefore, the answer is no."	Editorial states: "Why not test all febrile infants? The authors recognize that a major obstacle to urine testing is obtaining the specimen."
Ramage, 1995 An audit of the clinical management of urinary tract infection in childhood [286]	Assessed the in-patient and out-patient management of infants and children with documented symptomatic UTI.	1,826 patient episodes from a tertiary paediatric hospital in Glasgow, UK.	For a significant number of patients, the UTI diagnosis was made in the absence of culture confirmation, and following inappropriate urine sample collection.	Authors conclude: "These data reveal a continuing lack of uniformity in management practices in children with UTI and demonstrate the need for a wider application of practice guidelines".

Schroeder, 2005, Choice of urine collection methods for the diagnosis of urinary tract infection in young, febrile infants. [197]	Prospective cohort study. Study questions included (1) Which urine collection methods do clinicians use to diagnose UTI in febrile infants (2) What patient and clinicians characteristics influence the choice of urine collection method	Infants enrolled in the Pediatric Research in Office Settings' Febrile Infant Study. 219 practices from within the Pediatric Research in Office Settings' network. 3066 febrile infants aged 0-3 months.	Most urine samples were obtained by catheterisation (63% of urinalysis and 69% of urine cultures). Bag samples composed 31% of urinalysis and 24% of urine cultures.	Most pediatricians collect urine from febrile infants by catheterisation, but urine bags are also commonly used.
Selekman, 2016, Determinants of practice patterns in pediatric UTI management [198]	Email survey. Aimed to investigate practice patterns and factors influencing urine testing and antibiogram use for empiric antibiotic treatment of UTI in children, and ultimately to improve adherence to UTI guidelines.	Cross-sectional sample of physicians from various specialties caring for children. Included pediatricians, family practice physicians, pediatric emergency physicians, pediatric nephrologists and pediatric urologists. 47% response rate (366/777).	84% obtain a urine sample prior to treatment for UTI. Clinicians who did not always obtain urine would more be likely to order testing if the specimen were easier to collect (46%) and if results were available immediately (48%). Catheterisation was the preferred collection method, but urine collection by bag is common.	Most clinicians report following guidelines to obtain urine samples prior to antibiotic treatment for UTI. More clinicians would collect urine samples if the specimen was easier to collect.

Shah, 2008, Adherence to AAP practice guidelines for urinary tract infections at our teaching institution [195]	Retrospective chart review Aimed to evaluate adherence to AAP guidelines at a teaching hospital.	104 paediatric patients at a US hospital, median age 22 months	70% of urine samples were obtained by catheterisation, and the remainder by clean catch.	70% adherence to AAP recommendations for the method of urine collection.
EMERGENCY DEPARTMENT				
Study	**Study Type & Aims**	**Participants & Setting**	**Results**	**Summary**
Buntsma, 2012, How do clinicians obtain urine samples in young children? [142]	Online survey Assessed paediatric ED physician practice for urine collection for febrile children aged <24 months	Senior Emergency Physicians from 13 Australian/ New Zealand Paediatric EDs 60% response rate (109/183)	SPA was preferred for septic children <6 months Clean catch was preferred for children 7-24 months if febrile but well, catheter was preferred for children 7-24 months if febrile and unwell. Few clinicians would use bag urine collection for septic patients, but up to 25% would if the patient was relatively well	Showed variation in practice preferences for how to collect urine samples from young children. Up to 25% of clinicians would use urine bags in selected circumstances, against local guideline recommendations.
Geurts, 2014, Impact analysis of an evidence-based guideline on diagnosis of urinary tract infection in infants and young children with	Prospective cross-sectional observational study Aimed to implement and determine compliance with the Netherlands	Children 1-24 months, with unexplained fever (169 patients pre-intervention, 150 post intervention)	Compliance with the recommended initial diagnostic strategy was 25% pre-implementation and 47% after implementation of the guideline.	Found generally low compliance with local guideline recommendation to test urine samples in cases of unexplained fever, even after the implementation strategy.

unexplained fever [275]	national UTI guideline, using a multi-faceted implementation strategy.	Paediatric ED, Netherlands Primary outcome: collection of a urine culture using midstream, catheterisation, or SPA in all children with unexplained fever when the dipstick showed a positive result	Adherence specifically to urine collection method (with small numbers only), showed choice of collection method improved post-implementation.	Numbers relating to urine sample collection methods were small.
Ouellet-Pelletier, 2016, Adverse Events Following Diagnostic Urethral Catheterization in the Pediatric Emergency Department [165]	Prospective cohort study Telephone questionnaire Assessed adverse events associated with diagnostic catheterisation in young children.	199 parents of children 3-24 months who had in/out catheter performed in the ED. Tertiary Paediatric ED, Montreal, Canada.	21% reported a complication: - 10% dysuria - 8% genital pain - 6% urinary retention - 5% haematuria - 0.5% secondary UTI	Urethral catheterisation was associated with parentally reported adverse events in 21% of young children in the week following the procedure.
Spence, 2000, Diagnosing urinary tract infections in febrile infants and children: when evidence-based medicine and clinical practice collide [287]	Commentary on the impact of the AAP guidelines on practice in the Canadian ED setting.	Canadian ED setting.	The authors state: "Emergency physicians often view urinary catheterisation and bladder aspiration as invasive, uncomfortable and time consuming. Many are unfamiliar with SPA, concerned about its potential complications, and aware of its variable success rate."	The authors conclude that the AAP UTI guidelines may not be universally adopted.

PARENTS/CAREGIVERS				
Study	**Study Type & Aims**	**Participants & Setting**	**Results**	**Summary**
Liaw, 2000, Home collection of urine for culture from infants by three methods: survey of parents' preferences and bacterial contamination rates [136]	Study of parents' views on infant urine collection methods.	44 parents of children aged 1-18 months. Parents volunteered to collect urine at home by pad, bag, and clean catch in a randomised order, on one day.	Parents preferred pad and bag collection to clean catch 26/44 (59%) reported bag uncomfortable or distressing 36/44 (82%) found clean catch impractical or time-consuming 9/44 (20%) gave up on clean catch attempts, compared to 4/44 (9%) with bag and 1/44 (2%) with pad	Most parents preferred pad or bag collection compared to clean catch, which most found impractical or time-consuming. Over half reported urine bags were uncomfortable and distressing.
Owen, 2003, Parent's opinions on the diagnosis of children under 2 years of age with urinary tract infection [200]	Semi-structured questionnaire given to parents at first attendance (quantitative and qualitative data). Aimed to assess parental understanding of UTI in their child and identify any delay perceived in the diagnosis.	Parents of children <2yo referred after proven UTI. Outpatient paediatric department in Wales, UK. 52/84 parents responded (64%).	40% felt clean catch was the easiest method to collect a urine sample from their child, 37% bag, 23% pad. 54% found it difficult to collect urine. 84% had a sample collected before antibiotics started. Approximately half the respondents had received a leaflet about UTI and collecting urine, and had found this useful.	About half the respondents stated that they had had difficulty obtaining a specimen. Clean catch was the preferred non-invasive collection method. Content analysis of qualitative data identified key themes including: • Delay in requesting urine samples • Difficulties in collection • Information (leaflets) • Lack of awareness in health professionals

Selekman, 2017, Does perception of catheterization limit its use in pediatric UTI? [201]	Electronic, cross-sectional survey via social media (Facebook). Aimed to investigate parental perception of pediatric UTI evaluation, to better understand the factors that impede urine sample collection.	Parents of children with an history of UTI. 2726 respondents.	56% of parents perceived extreme distress with catheterisation.	Authors conclude "it is clear parental input may have a substantial impact on the method of evaluation of their child's suspected UTI."

11.7 ECONOMIC EVALUATION SUPPLEMENTARY DATA

11.7.1 Additional costs data

Table 16: Hospital time and costs data (RCH 2016 calendar year)

	UTI	PUO
Non-admitted patients (only seen in ED)		
Number	167	290
Mean time in ED	240 minutes	246 minutes
Mean time occupying ED cubicle	156 minutes	155 minutes
Total costs	$73,306	$130,951
Average cost per presentation	$439	$452
Admitted patients (seen in ED and admitted to hospital inpatient ward)		
Number	173	322
Total costs	$226,485	$1,588,831
Average cost per presentation	$1356	$4934

Hospital costs data was obtained from the RCH Decision Support Unit for patients aged 0-24 months with an ICD-10 code indicating a primary diagnosis of UTI or unexplained fever (PUO).

Table 17: Urine laboratory cultures (RCH 2016 calendar year)

	ED	WARD	TOTAL
Bag	9 (<1%)	22 (2%)	31 (1%)
Clean Catch	1384 (78%)	540 (37%)	1924 (60%)
Catheter	200 (11%)	489 (34%)	689 (21%)
SPA	122 (7%)	68 (5%)	190 (6%)
Method unstated	61 (4%)	319 (22%)	380 (12%)
Other	0	11 (1%)	11 (<1%)
Total	1776	1449	3225

Hospital laboratory data was obtained from the RCH Pathology Department for patients aged 0-24 months who had a urine culture performed.

Apparent discrepancy in total % for ward column due to rounding

Assumed if documented as "midstream" from child 0-24 months this was a clean-catch collection from a pre-continent child

Other: e.g mitrofanoff or ureterostomy sample

Table 18: Australian hospital episodes for UTI - total and average costs

	Number	Total Cost	Length Of Stay	Average cost
Admitted acute	4,831	$ 54,617,023.79	5.2 days	$11,305.53
Admitted ED	1,855	$ 1,574,467.03	N/A	$848.77
Non-admitted ED	3,021	$ 1,641,401.13	N/A	$543.33
Total	9,707	$ 57,832,891.96		$5957.85

Hospital episodes for children aged 0-24 months with ICD-10 code for principal or additional diagnosis of UTI. Data obtained from the Independent Hospital Pricing Authority (IHPA) for the 2015/16 financial year.

Table 19: Australian hospital episodes for PUO - total and average costs

	Number	Total Cost	Length Of Stay	Average cost
Admitted acute	4,605	$ 60,449,039.86	5.65 days	$13126.83
Admitted ED	6,747	$ 6,354,172.47	N/A	$941.78
Non-admitted ED	7,210	$ 3,604,570.38	N/A	$499.94
Total	18,562	$ 70,407,782.72		$3793.11

Hospital episodes for children aged 0-24 months with ICD-10 code for principal or additional diagnosis of pyrexia of unknown origin. Data obtained from IHPA for the 2015/16 financial year.

11.8 KNOWLEDGE TRANSLATION SUPPLEMENTARY DATA

11.8.1 Indirect knowledge translation outputs

Table 20: KT - Published reviews and media

PUBLISHED REVIEWS
>10 published reviews, editorials and commentaries highlighting the Quick-Wee method, including: **PRIMARY CARE** - *The BMJ* (UK) [123] - *The Journal of Family Practice* (US) [314] - *Canadian Medical Association Journal* (Canada) [312] **PAEDIATRICS** - *Journal of Paediatrics & Child Health* (Australia) [315] - *Archives of Disease in Childhood Education & Practice* (UK) [311] - *The Journal of Pediatrics* (US) [313] **EMERGENCY MEDICINE** - *The Journal of Emergency Medicine* (US) [316] - *Advanced Emergency Nursing Journal* [317] **RESOURCE LIMITED SETTINGS** - *Indian Pediatrics* (India) [318]
MAINSTREAM MEDIA
PRINT MEDIA 2 articles in mainstream newspapers: the Herald Sun (Victoria) and the Daily Telegraph (NSW) **ELECTRONIC MEDIA** Feature article (click hyperlink to view) and video in Pursuit, University of Melbourne
MEDICAL MEDIA
>20 medical media and further online mentions including: **GENERAL** - NEJM Journal Watch: Medical news and article summary (US) - Reuters Health: Health information report (US) - TRIP (Turning Research Into Practice) database: Latest & greatest articles (UK) **PRIMARY CARE** - *American Family Physician*: Top patient oriented evidence that matters (POEMs) of 2017 (US) - *Australian Doctor*: Feature article (Australia) - Red Whale GP Updates & Handbooks: Top 10 2017 papers (UK)

PAEDIATRICS
- *Archives of Disease in Childhood*: Highlights from the literature (UK)
- College of Physicians and Surgeons of British Columbia: Cites and bytes 2017 (Canada)
- Victorian Public Healthcare Awards Showcase 2017 (Australia)
EMERGENCY MEDICINE
- Royal College of Emergency Medicine: Learning Summary June 2017 (UK)
- *Journal of Urgent Care*: Abstract summary June 2017 (US)
- Australasian Society for Emergency Medicine: Abstract summary 2017 (Australia)
RESOURCE LIMITED SETTINGS
- Emergency Medicine Kenya Foundation: Online summary (Kenya)

Examples of knowledge translation outcomes and impact, incorporating quantitative metrics and qualitative data for each target group and key outcome, are summarised below in Tables 21-24. Reach and impact data is provided were this was accessible to the doctoral candidate, with data reported as of September 2019.

Table 21: KT - Parent and carer user outcomes

OUTCOME: AWARENESS OF QUICK-WEE METHOD
Featured in Australia mainstream media in the Herald Sun and Daily Telegraph.
- reaching audience of >370,000 (Isentia media monitoring)
Featured in Pursuit article, University of Melbourne
- >60,000 views via webpage and YouTube
Featured blog post on parenting websites MamaMia (Australia) and Babycentre (UK)
- >40,000 page views and >20,000 page views respectively
OUTCOME: ACCEPTANCE OF QUICK-WEE METHOD
The method had higher parental satisfaction ratings than standard clean catch in two published studies in the hospital setting. Qualitative data indicates the method is also highly acceptable to parents in general practice.
"Parents and clinicians reported greater satisfaction with the Quick-Wee method, suggesting it was a more acceptable experience of sample collection than the standard clean catch technique." [123]
OUTCOME: USE OF QUICK-WEE METHOD
Royal Children's Hospital Kids Health Information Website Fact Sheets: UTI & Urine Samples
- >130,000 page views

Table 22: KT - Clinician outcomes

OUTCOME: AWARENESS OF QUICK-WEE METHOD
Published in a highly visible and influential journal, >90,000 direct views - 35 citations, field weighted citation index 4.35 - Altmetric score of 342 (top 1% of research outputs ever tracked) - wide online & social media coverage on medical and nursing sites in >30 countries - >500 tweets (including by key medical opinion leaders) reaching >1,000,000 followers **Features in a range of other clinical resources** - learning resources from the Royal College of Emergency Medicine (UK), American College of Emergency Medicine (US), American Association of Pediatrics (US) - multiple print and digital "Evidence Highlights" internationally (Australia, UK, US, Canada, Ireland, India, Croatia, Spain, France, Finland, Kenya) - 3 textbooks: Textbook of Paediatric Emergency Medicine (Elsevier 2018), Advances in Pediatrics (Elsevier 2018) & Nelson's Textbook of Pediatrics (Elsevier 2019)
OUTCOME: ACCEPTANCE OF QUICK-WEE METHOD
The method had higher clinician satisfaction ratings than standard clean catch in two published studies in the hospital setting, with further qualitative evidence the method is highly acceptable to clinicians in primary care. "The Quick-Wee method is a quick and easy intervention that we can teach our practice nurses and/or employ ourselves. I'll definitely be trying this next time I need to catch a urine sample from a tricky paediatric customer." [319]
OUTCOME: USE OF QUICK-WEE METHOD
Several clinicians in the preceding qualitative study (Paper 6) reported using the Quick-Wee method: "Since I learned of the Quick-Wee method, I have been trying it" [309]

Table 23: KT – Researcher outcomes

OUTCOME: ADOPT/ADAPT QUICK-WEE METHOD IN OTHER STUDIES
Features in 3 current clinical trials (based on trial database searches and personal correspondence from other researchers).
IMPACT CASE STUDY
The Ultra-Wee RCT is listed on the Clinicaltrials.gov trials database. Ultra-Wee uses cold stimulation and gentle suprapubic pressure from ultrasound bladder volume evaluation to stimulate voiding, adapting the cold saline soaked gauze cutaneous stimulation used in the Quick-Wee RCT.

Table 24: KT – Policy maker outcomes

OUTCOME: AWARENESS OF QUICK-WEE METHOD
Featured in a 'NIHR Signal' report: National Institute for Health Research (important research summary sent to clinicians and decision makers across the UK) https://discover.dc.nihr.ac.uk/content/signal-000489/placing-wet-gauze-on-babies-tummies-speeds-up-urine-collection
OUTCOME: ACCEPTANCE AND USE OF QUICK-WEE METHOD
Featured in Public Health England: Diagnosis of urinary tract infections: quick reference tool for primary care (policy guidance for use and adaptation in primary care, endorsed by the Royal College of General Practitioners, UK) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829721/Diagnosis_of_urinary_tract_infections_UTI_diagnostic_flowchart.pdf
IMPACT CASE STUDY
Based on published evidence of effectiveness, cost-effectiveness and acceptability, policy makers in the UK have begun to incorporate the Quick-Wee method into policy documents and clinical practice guidelines. The Quick-Wee research has been disseminated via a NIHR signal report, included in national primary care policy, and subsequently incorporated into NHS hospital and county guidelines (outlined in Chapter 8).

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