The socio-economic value of diagnostic innovation - managing paediatric fever in the Emergency Department

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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Declaration

The material within this thesis is my own work, it has not been presented, nor is currently being presented, either wholly or in part for any other degree or qualification.

Dedication

I would like to dedicate this thesis to my close friends and family, for their constant patience, reassurance, and support. To Max, Liz, and Tim, for providing me the opportunity to work flexibly throughout the course of my doctoral studies and allowing me to put both education and family first. To Rebecca, for accepting the long hours and frequent absences from home life, and for continually pushing me to get over the line, including staying up late with me just to keep me company while I write. To Harry, Abigail, and Persephone, for giving perspective, being exceptionally patient, and being a fantastic but completely worthwhile distraction throughout this experience. Above all others, this thesis is for you.

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Abstract

Introduction: Ensuring the appropriate and most beneficial use of healthcare resources is a public health imperative. But so too is assuring that care quality is not measured solely by clinical or economic aspects of care but also by the entire patient experience. This thesis examines the economic and patient/parent-centric impact of managing a highly common condition, paediatric febrile illness, in Emergency Department (ED) settings. The chapters included explore the impact of paediatric febrile illness to patients, parents and health services alike, while also exploring the potential value of diagnostic and care-pathway innovations designed to reduce the incidence and impact of diagnostic uncertainty in the management of this highly common condition.

Methods: Utilizing a series of rich cross-sectional, qualitative, and patient-centric datasets from the North West of England, I analyse, for the first time in this field, the combined economic, and patient/parent-centric impact of the ED management of paediatric febrile illness; using generalised linear, mixed logit and stochastic economic modelling techniques. All chapters adjust for both confirmed, and potentially clinically important covariates, including extensive analysis of uncertainty where possible. Following an introduction and an extensive literature review of studies examining the economic impact of paediatric febrile illness in ED-settings, Chapter 3 explores this subject, based on established care pathways. This study uses novel time-driven and activity-based micro-costing (TDABC) techniques to explore the impact of patient age, triage status, gender, clinical role and experience and other clinical

parameters on healthcare utilisation. Chapter 4 explores and compares both parental and healthcare professional's (HCPs) preferences for the management of paediatric febrile illness in ED-settings, using an economic mixed-methods approach. Following an iterative methodology of literature review, focus-group research, coin-ranking exercises and a discrete-choice experiment; this thesis performs an in-depth exploration of satisfaction with existing care pathways. In doing so, the findings quantify the potential value of diagnostic innovations, including point-of-care (POC) testing, accounting for differences in preferences among heterogeneous parental and health care professional (HCP)-groups. Chapter 5 employs a prospective cohort-control design to examine the potential role of GP-led management for non-urgent ED admissions including paediatric febrile illness, comparing key economic, operational (including waiting times), and clinical outcomes (including antimicrobial prescribing) versus existing care pathways. Finally, Chapter 6 utilises a decision tree approach to combine the findings of the previous chapters. It explores the potential economic and patient-centric value of a range of exploratory scenarios to improve the management of paediatric febrile illness in ED-settings, including POC-testing, GP-led management and both combined. The findings of this chapter highlight the factors most influential in determining the comparative cost-effectiveness of each strategy, providing recommendations for future implementations.

Results: The findings of this thesis suggest that the management of paediatric febrile illness within EDs, imposes a substantial economic burden. Costs are driven predominantly by diagnostic uncertainty, which manifests itself as increases in observation time, clinically unnecessary antibiotic use, and prolonged inpatient

admission. Children aged 0-6 months, those triaged as Manchester Triage System (MTS) yellow and above, and those managed by newly qualified doctors are the most likely to use additional resources in the ED. Ironically, the stepped-cautious approach often used when investigating paediatric febrile illness is also a key contributor to parental and HCP dissatisfaction with care. Prolonged waiting times induce significant concern, anxiety, and a fear of deterioration, while invasive investigations including venepuncture cause discomfort to children, which in turn affects parents. Receiving a faster diagnosis which improves confidence, and reduces uncertainty, is therefore a major benefit to both parents and HCPs, and this may be achieved via the use of novel, cutting edge rapid diagnostic technologies, such as host or pathogen molecular diagnostics, omics-driven approaches at the bedside, or POC-testing. Additionally, modifications to existing care pathways, such as GP-led management of non-urgent ED attendances may also be of significant benefit. While the latter is likely to improve operational and economic outcomes considerably, GP-led management may also inadvertently lead to increases in antimicrobial prescribing, if not accompanied by antimicrobial stewardship initiatives, which have proven highly successful in other settings. Given the importance of reducing clinically unnecessary antibiotic use, this may limit the utility of this strategy for the management of paediatric febrile illness in ED-settings; while factors including adherence to results, sensitivity and the cost of any POC-test, are also likely to limit the effectiveness of these diagnostic advances.

Conclusions: Paediatric febrile illness, while common, is a clinical conundrum, and often necessitates a cautious approach, characterised by interventions which provide limited diagnostic value. Diagnostic uncertainty is a key orchestrator of febrile illness

pathways, with certain populations, namely infants, and those triaged as MTS yellow or higher, most likely to receive potentially avoidable interventions, at the expense of reduced parental and HCP satisfaction with care. Policies to reduce the impact of diagnostic uncertainty, including GP-led management and POC-testing, are likely to improve economic, clinical, and patient-centric outcomes significantly, particularly if used in combination. Associated benefits are likely to be highest if such technologies and care pathways are tailored to those where the perceived risks of failing to identify potentially life-threatening bacterial infections are greatest.

Contents

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Abbreviations

95% CI	95% confidence interval
AB	Antibiotic
AMR	Antimicrobial resistance
ANP	Advanced nurse practitioner
ARI	Acute respiratory infection
BPM	Beats per minute
BS	Bacterial syndrome
CA-LCI	Community acquired laboratory-confirmed influenza
CEAC	Cost effectiveness acceptability curve
COPD	Chronic obstructive pulmonary disorder
CRP	C-reactive protein
CSF	Cerebrospinal fluid analysis
CT	Computerised tomography
CT1-3	Core training years 1-3
DARE	Database of abstracts of reviews and effects
DB	Definite bacterial infection
DCE	Discrete-choice experiment
DV	Definite viral infection
ECG	Electrocardiogram
ED	Emergency department
ENT	Ear, nose, and throat
ESR	Erythrocyte sedimentation rate
EU	European union
FBC	Full blood count

FWS	Fever without source
GLM	Generalised linear model
GP	General practitioner
HCP	Healthcare professional
HES	Hospital episode statistics
HPIV	Human parainfluenza virus
HR	Heart rate
HRG	Healthcare resource group
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICS	Integrated care system
IMD	Index of multiple deprivation
IQR	Interquartile range
ISPOR	International society of pharmaco-economics and outcomes research
IV	Intravenous
LDC	Lesser developed country
LFT	Liver function test
LRTI	Lower respiratory tract infection
MTS	Manchester triage system
NHS	National health service
NHSEED	National health service economic evaluation database
NICE	National institute for health and care excellence
OR	Odds ratio
PB	Probable bacterial infection
PCR	Polymerase chain reaction

POC	Point-of-care test
PSA	Probabilistic sensitivity analysis
PTA	Parent teacher association
PV	Probable viral infection
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Respiratory rate
RSV	Respiratory syncytial virus
RTI	Respiratory tract infection
RUT	Random Utility Theory
SBI	Serious bacterial infection
SD	Standard deviation
SOC	Standard of care
ST1-3	Specialised training years 1-3
ST4-7	Specialised training years 4-7
TDABC	Time-driven and activity-based costing
UK	United Kingdom
URTI	Upper respiratory tract infection
USA	United States of America
UTI	Urinary tract infection
VS	Viral syndrome
WTP	Willingness-to-pay
WTW	Willingness-to-wait

Chapter 1: Introduction

Clinical presentation of febrile illness and relevance of the issue

Fever has long been among the most common causes of presentation to paediatric EDs (Boyle, Smith and McIntyre 2000). In 1991 it was estimated that fever was a presenting complaint in approximately 20% of all visits to paediatric EDs in the United States (Alpern and Henretig 2006). This was followed up by a study, conducted in 2006 in a general hospital in Liege, Belgium, demonstrating that 22.1% of 11,483 consecutive paediatric ED attendances were a result of fever in children; (Massin, et al. 2006) while studies from the United Kingdom (UK), suggest a figure of around 14%. (Van den Bruel and Thompson 2014) (Sands, et al. 2012)

From an epidemiological perspective, otherwise well children can be expected to experience several episodes of fever per year, particularly among those under the age of five, after which incidence rates fall considerably. Country-specific reports from cross-sectional surveys have suggested a worldwide incidence of between two and nine febrile episodes per year in children under age five years of age (Herlihy, et al. 2016). A review by D'Acremont provided a consolidated figure of 5.88 fever episodes per year (D'Acremont, et al. 2016), suggesting that on average, children under the age of five can be expected to suffer from fever approximately once every two months.

Additionally, while the causes of fever are predominantly viral in nature, (Animut, et al. 2009) (Colvin, et al. 2012) (Hagedoorn, et al. 2020) the aetiological spectrum of

febrile illness is diverse, ranging from invasive bacterial infections (Hagedoorn, et al. 2020) to trauma, and even neoplasms (Limper, et al. 2011). This broad spectrum of possibilities when fever arises results in uncertainty, and consequentially, concern among parents (Teagle and Powell 2014). Kai et al. conducted a survey of parents' responses to acute illness in their children and found that fever, cough and the possibility of meningitis were among parents' primary concerns when their children became acutely ill (Kai 1996). While in scientific terms, fever is a natural response to infection and is not harmful in itself; parents are often worried that febrile illness might herald potential harm, including the development of meningitis or seizures (Kelly, et al. 2016) (Jones and Jacobsen 2007), or permanent impairment of some kind, including brain damage (Ravanipour, Akaberian and Hatami 2014), sepsis, or even death. Parents also express concern that the presence of fever itself may harm their children (Crocetti, Moghbeli and Serwint 2001), a concern which increases with the extent of the fever, and may be compounded by the possibility of being unable to adequately determine the 'normal' temperature of their child. Additionally, a high confidence in the quality and investigative ability of ED care (Butun, Linden and Lynn 2019); and seeing fever as the condition to be managed, rather than as signifying something which is typically much more benign; it is understandable why ED presentations attributable to paediatric febrile illness are so common.

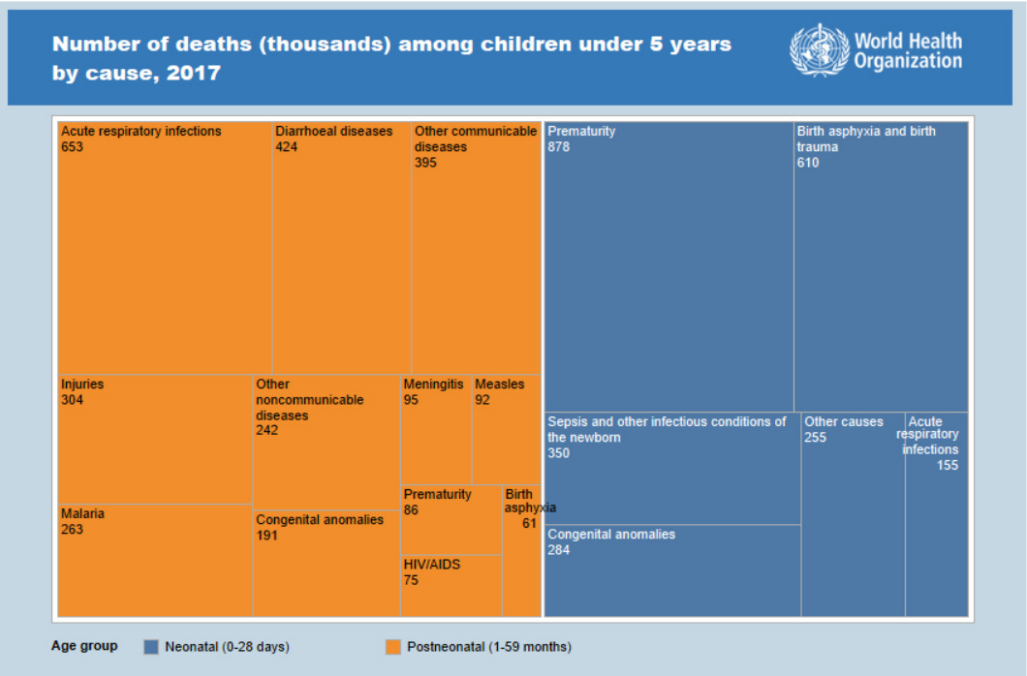
The increasing trend for parents to visit EDs with febrile children, has inevitably resulted in increases in 'overflow' pressures elsewhere in healthcare systems. In a study including one percent of the national child population of the UK, infections and respiratory disorders accounted for approximately 40% of primary care consultations

(Grin, 2001). Similarly, in a national study consisting of approximately 10,000 childhood presentations to general practice in the Netherlands, annual consultation rates for fever among those aged less than 12 months were 60%, 36% in those aged 1-4 years, and 20% among those aged 5-15 years (Gu, 2001). Equally, out-of-hours care has also become a common point of contact for paediatric febrile illness, with a Dutch study conducted in a single GP out-of-hours service (de Bont, et al. 2015), demonstrating that childhood fever was the presenting complaint in approximately 14.6 contacts with GP out-of-hours services per day. In the UK, similar figures have been observed, with an estimated 64% of out-of-hours calls for children under the age of five related to fever (Dale, Crouch and Lloyd 1998). A more recent evaluation suggested fever was the third most common presenting symptom in a study of 18,987 children attending out-of-hours services in Oxfordshire, England (Edwards, et al. 2020).

The role of diagnostic uncertainty

Most HCPs are aware that infectious diseases were, and continue to be, an important cause of mortality and morbidity in childhood, as the World Health Organization reports (Figure 1).

Figure 1: Causes of death among children reported by the World Health Organization



World Health Organization Global Health Observatory Data (2017)

Despite childhood mortality falling considerably in recent years, due to advances in immunisation, other prevention efforts and treatment estimates suggest that infections still account for one-in-five childhood deaths in England and Wales (Ferreras-Antolín, et al. 2019). Respiratory tract infections are the most common presentation (Ferreras-Antolín, et al. 2019). While most causes of fever in children will be self-limiting (Barbi, et al. 2017) (Manzano, et al. 2011), fear of failing to identify rare (<1%) (Van den Bruel, Aertgeerts, et al. 2007) but life-threatening infections among children with fever, remains a persistent problem for clinicians.

Among febrile children who present with a clear viral or bacterial focus of infection, such as an inflamed tympanic membrane, in the case of acute otitis media; or red,

inflamed tonsils with purulent exudate in the case of tonsilitis, uncertainty is minimal, and therefore diagnosis is often straightforward, and treatment initiated immediately thereafter. However, in approximately 8% of cases, fever is the only presenting symptom, with no other distinguishable or apparent cause (Borensztajn, et al. 2021), a condition known broadly as “fever without source” (Baraff 2000). Clinical concern in the management of this group is high, and caution strongly advised. This is because different causes of fever, including clinically benign viral illnesses, bacterial, or even potentially life-threatening “occult” severe bacterial infections (Irwin, Drew and Marshall 2015), can, and often will result in almost identical clinical presentations in paediatric patients. This makes diagnosis of a cause of fever based on clinical judgement, patient history, physical assessment, and presenting symptoms alone, a significant challenge. This is particularly true among infants and as such, it is not uncommon to undertake numerous investigations among children aged <3 months (NICE 2017).

Economics, operational efficiency, and the diagnostic void in paediatric febrile illness

A paucity of timely and sufficiently accurate diagnostics can add to the difficulty in effectively, efficiently, and safely managing the febrile child. In the absence of clear clinical findings to suggest a definitive or even plausible cause, blood cultures remain the gold-standard of laboratory diagnosis of bloodstream infections (BSIs) in infants and children (Lamy, et al. 2016), and are recommended for use among all infants with fever within recent NICE guidance on the management of fever in under 5s (NICE 2017).

However, blood cultures typically take 12-48 hours to result (Lambregts, et al. 2019), but can take up to 72 hours for a final result, (Pardo, et al. 2014) and have a sensitivity of just 30-40% (Martinón-Torres, et al. 2018), due to slow-growing microbes, prior antibiotic exposure, and non-cultivatable pathogens, (Scerbo, et al. 2016). Blood cultures also have a significant false positive rate, because of contamination with commensal bacteria from the skin and mucosal surfaces (Weddle, Jackson and Selvarangan 2011). This limits the real-time diagnostic utility of the blood culture to clinicians who are required to make decisions concerning the management of the febrile child in real time. This is of particular concern when considering that every hour for which serious but "hidden" invasive bacterial conditions are left unnoticed, and ultimately, untreated, increases the possibility of serious and potentially life-threatening or limiting complications developing (Irwin, Drew and Marshall 2015) (Gangoiti, et al. 2018).

Considering the practical limitations of existing diagnostic modalities, coupled with the knowledge that paediatric febrile illness could be indicative of a range of potential conditions of varying clinical severities, a cautious-stepped approach to the management of the febrile child is therefore common. This approach has been reported elsewhere as being a valuable tool for the management of infants with fever without source in the emergency department (Gomez, et al. 2016), confirming its superior accuracy in identifying invasive bacterial infections. This approach, in general, is characterised by extended periods of repeated observation, ancillary investigations, radiography, and the precautionary use of antibiotics, often prior to definitive evidence of bacterial foci (Nijman, et al. 2013), and is generally more frequent among paediatric

emergency clinicians than general emergency clinicians (Issacman D J 2001). This iterative approach is common given its recommendation within NICE guidelines, which suggest that at least among children aged <3 months, a full blood count, blood culture, CRP, urinalysis and x-ray (in the case of respiratory symptoms) are all required (NICE 2017). However, the practical extent to which clinical teams err on the side of caution is also subject to considerable variation. A 2019 study highlighted significant differences in local, regional and national aspects of care for febrile children across Europe (Borensztajn, et al. 2019). Six of the 11 hospitals in this study had guidelines regarding the time a child could stay in the ED, after which they should be admitted or discharged. While guidelines advising not to take a cautious stepped approach are uncommon, the time permitted for clinical teams to undertake investigations to determine an aetiology of fever was subject to considerable variation, ranging from three to 24 hours. These difference would, in turn, not only the ability of ED staff to determine a likely cause of fever, but also the economic impact of any treatment provided.

Therefore, while cautious, and considered to be the safest course of action, this approach can also result in several disadvantages. These interventions are invasive, can be painful, may prolong visit times, extend ED waiting times, contribute to antimicrobial resistance (AMR), and increase the use of already scarce ED healthcare resources, for what could potentially be minimal clinical benefit. Additionally, overcrowded ED waiting rooms may add to any stress or anxiety already experienced by concerned parents, while waiting for their child to be seen. (Embong, et al. 2018)

With the potential over-treatment of febrile children on the one-hand, and the prospect of failing to identify potentially life-threatening SBIs on the other; both parents and clinical teams are left with a difficult choice. While the costs of failing to identify serious bacterial infections are high, so too are the costs associated with the "overtreatment" of children who will predominantly be suffering from clinically benign viral illnesses, in the pursuit of identifying the rare needle (bacteraemia) among the febrile haystack. Although much less immediate and much less noticeable, when compared to the estimated ~£1.3m lifetime treatment costs associated with caring for those with missed diagnosis of severe meningococcal disease (Wright, Wordsworth and Glennie 2013); in addition to the lifetime loss in quality-adjusted life years (QALYs) and the impact on caregivers; the associated costs, in terms of staff time, use of radiology, AMR and healthcare financing, are nonetheless significant and potentially avoidable.

Given the high incidence and likelihood of ED presentation for those with paediatric febrile illness, the result is that existing stepped-management pathways for investigating causes of fever in children, which rely on existing diagnostic modalities, may account for a similar, if not greater economic burden, than those associated with rare serious adverse events. Except for a handful of studies conducted between six and 25 years ago, and predominantly in a US-setting (Byington, et al. 2012) (Schriger, et al. 2000); to date, this subject, has received little scientific attention. As such, the real-world economic burden of managing this highly common condition in ED-settings, is currently unclear.

The importance of information: could diagnostic advances improve care?

In a time where fast, efficient, and personalised care has become increasingly important, POC tests, which have been both successful (Hays, et al. 2019) (Briel, et al. 2006) and well received (Cals and van Weert 2013) within primary care, may be one solution to achieving a more appropriate and measured use of healthcare resources within EDs, while at the same time, ensuring patient, carer and HCP satisfaction with care.

Several readily available POC tests have shown promise in the diagnosis of a variety of infectious diseases, including those measuring capillary C-reactive protein (CRP) (Mintegi 2018) (Hernandez-Bou, et al. 2017) (Butler, Gillespie and White 2019) (Francis, et al. 2020) (Little, et al. 2019), whole blood procalcitonin (Waterfield, et al. 2018) (van Vugt, et al. 2013), and lactate (Goyal, et al. 2010). Use of these technologies may not only limit the emergence and global spread of antimicrobial resistant microorganisms (Bell, et al. 2014), but may also be cost saving (Roulliaud, et al. 2018), decrease waiting times in otherwise overcrowded EDs, and increase parental/carer satisfaction.

This is because decisions made during the management of paediatric febrile illness not only mitigate diagnostic uncertainty, but may also contribute to patient, carer and HCP satisfaction with the care provided. For example, parental anxiety and fear of serious but rare illness including sepsis (Wilson, et al. 2019), can result in the expectation for antibiotics, even when not clinically indicated (Rousounidis, et al. 2011) (Mustafa, et al. 2014). Similarly, some may prefer their child to be managed by a more experienced clinician (Chen, Zou and Shuster 2017), which may not always be possible in crowded

EDs, and may require clinical teams to manage the expectations of parents. With the continued development of more sensitive, accurate and faster diagnostics, including molecular diagnostics and protein biomarkers, processes and experiences when investigating febrile illness are likely to change. Although reductions in waiting times may be preferred, a reduced likelihood of receiving antibiotics, or a reduction in the use of ancillary investigations, may result in dis-satisfaction among some parents and healthcare providers. While POC-testing may therefore potentially improve the efficiency of the management of paediatric febrile illness, what is unclear, are the expectations of parents and HCPs alike when managing paediatric febrile illness. Specifically, it is unclear how the eventual introduction of novel technologies will disrupt established care processes and impact on patient and HCP 'satisfaction' with care. Finally, while most POC-tests undergo clinical performance assessment, only a small number to date (Butler, Gillespie and White 2019), have evaluated their broader impact on operational, economic, and preference-based outcomes (Verbakel, et al. 2017). As such, the real-world value of POC-testing for paediatric febrile illness in ED-settings, beyond the clinical trial, remains largely unclear.

Gaps in the scientific literature

While there is developing literature on the management of paediatric febrile illness, clear gaps in knowledge remain. Firstly, the economic impact of managing paediatric febrile illness in ED-settings is currently unknown, in large part because of the substantial variation in approaches to managing paediatric febrile illness among different health systems. This was reported in a 2019 study published as part of the

PERFORM work package (Borensztajn, et al. 2019), where, across eleven EU countries, guidelines used for managing fever were very different. Three of these countries used NICE guidelines, with the other eight using variations of local guidelines. This difference was also exacerbated by differences in the triage systems applied, and the level of specialty training of supervising clinicians. Taken together, this results in a paucity of information at a global level, regarding the precise economic impact of managing paediatric febrile illness in ED settings. While studies predominantly conducted in US-settings have explored healthcare costs among specific subsets of the febrile spectrum, including those with meningococcal disease (Hoberman, et al. 1999), URTIs (Bell, et al. 2015) or laboratory-confirmed influenza (Iyer, et al. 2006), no study has to date assessed the economic impact of managing paediatric febrile illness of all causes, in ED settings. This leaves a gap in understanding when considering what the expected impact or benefit of improved diagnostics may be, as the economic impact of the current standard of care remains unclear. Secondly, it is currently unknown which patient and healthcare provider characteristics affect healthcare resource utilisation, and as a result, where diagnostic advances may be likely to unlock the greatest clinical and economic benefit, whether among infants, those considered less urgent following triage, or those managed by doctors in postgraduate training.

Thirdly, perspectives regarding the management of paediatric febrile illness are also unclear. Making changes to care pathways not only has the potential to impact health-service efficiency and patient outcomes, but also satisfaction, both with the care received (parent/carer perspective), and with the care provided (HCP perspective). In

an era of patient-centric medicine, any changes to care pathways which involve the inclusion of novel diagnostic modalities, whether via POC-testing or other means, should aim take these perspectives into account. Given that changing diagnostic processes are likely to impact several components of care pathways, including waiting times, the number, and duration of interactions with HCPs, and whether patient samples including blood, urine, saliva or stool are required, it is likely that these changes will impact, whether positively or negatively, the 'utility' or satisfaction with care versus what is currently experienced today. Though not a dominant consideration which would override clinical decision making; given the importance of patient-centric care in modern-day NHS decision making, it is important that this area is researched to understand the potential trade-offs between any economic, operational or clinical improvements and changes in patient/carer and HCP satisfaction with the care provided.

Additionally, the literature around the role of 'extended access' and other alternative measures to manage increasing ED demand, is still in its infancy. While many ED attendances citing fever undoubtedly result from what is perceived as an acute medical problem, it is likely that many may not require immediate specialized emergency medical care. Increased concern regarding the potential severity of conditions, parental anxiety, and a perceived need for urgent treatment (Butun, Linden and Lynn 2019) (Smith and Roth 2008) (Williams, O'Rourke and Keogh 2009), which are common within childhood fever, may exacerbate this problem, as can difficulty in obtaining primary care appointments. While the benefits of introducing GPs in EDs for

managing non-urgent cases are well documented, and include increased patient satisfaction, reduced waiting times, and reductions in invasive examinations; it is unclear whether this represents an efficient use of NHS resources, with the only economic analysis to date taking place in 1996. Additionally, no study has conducted an assessment of the impact of measures such as GP in ED models of care for those with paediatric febrile illness, how care processes, the role of ancillary investigations, radiography and antibiotics differs between specialist (ED) and general (GP) clinical teams, and how this may affect both outcomes and healthcare costs for those with paediatric febrile illness.

Finally, taking each question above into account, it remains unclear how cost-effective modifying existing care pathways for the management of paediatric febrile illness is likely to be. Questions around the financial impact of the existing standard of care, populations with the greatest likelihood of receiving benefit from improved diagnostics, and those around how acceptable any changes are likely to be for parents and HCPs alike; may all be summed into this one overarching question. Can POC-testing improve the cost-effectiveness of the ED management of paediatric febrile illness, and what are the factors which are most influential in determining this outcome?

The studies in this thesis aim to fill these important gaps in our understanding of the current management and opportunities for improvement for those attending the ED with paediatric febrile illness; by utilizing a series of rich cross-sectional and qualitative, patient-centric datasets from a tertiary children's hospital in North West England. A key question in this thesis is to clarify existing care pathways for the

management of paediatric febrile illness, and determine both the financial, HCP and patient-centric impact of these. In doing so, we aim to highlight any opportunities for improvement; not only in clinical, economic and operational outcomes, but also satisfaction with care. By including satisfaction with care as part of our assessment and "success" criteria the approach utilised within this thesis differs slightly from the usual approach of informing assessments of cost-effectiveness through the use of a cost-utility analysis. It is important to evaluate the many ways in which changing care pathways may ultimately impact patients and the healthcare system in which they are intended for use. As part of the PERFORM work package, this additional perspective, taking a cost-utility approach, informed by quality-adjusted life years (QALYs) is being performed by a separate PhD researcher.

Finally, while conducted primarily within a single institution in the North West of England, the findings of these studies are intended to provide generalizable insights, or at least enable well-informed hypothesis generation, regarding the opportunity for clinical, economic, operational and patient-centric improvements in care processes, in the event of diagnostic advancement for identifying infectious diseases.

Aims & Objectives of the research

The aim of the PERFORM (Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management Across the European Union) (PERFORM 2016) is to identify, and validate promising new discriminators of bacterial and viral infection including transcriptomic and clinical phenotypic markers. The most accurate markers distinguishing bacterial and viral infection will be evaluated in prospective cohorts of patients reflecting the different health care settings across European countries. By

linking sophisticated new genomic and proteomic approaches to careful clinical phenotyping, and building on pilot data from our previous studies the PERFORM work package will aim to develop a comprehensive management plan for febrile patients which can be rolled out in healthcare systems across Europe. A large part of this process, which this thesis specifically contributes to, is the demonstration if potential impact and value of any resulting changes to care pathways, and how these affect operational, clinical, economic and social indicators of treatment success. The overall aim of this thesis therefore, is to investigate the potential impact that POC-testing, or alternative advancements in infectious disease diagnostics, may have on the ED-management of highly common, paediatric febrile illness. To this end the main objectives of this thesis are to answer the following questions:

1. What is the economic impact of the ED-management of paediatric febrile illness? How much healthcare resource is dedicated to this and what role does diagnostic uncertainty play in this process?

2. Which groups of children consume the greatest level of resources and how does this differ with respect to differing characteristics of the child and the treating clinician? Can differences in treatment costs be explained?

3. What matters to parents when their children are being cared for with fever in the ED, and similarly, what matters to the HCPs providing care? How would changing care processes, through the introduction of POC testing for example,

affect overall satisfaction with care, and its value for patients, parents, and healthcare providers?

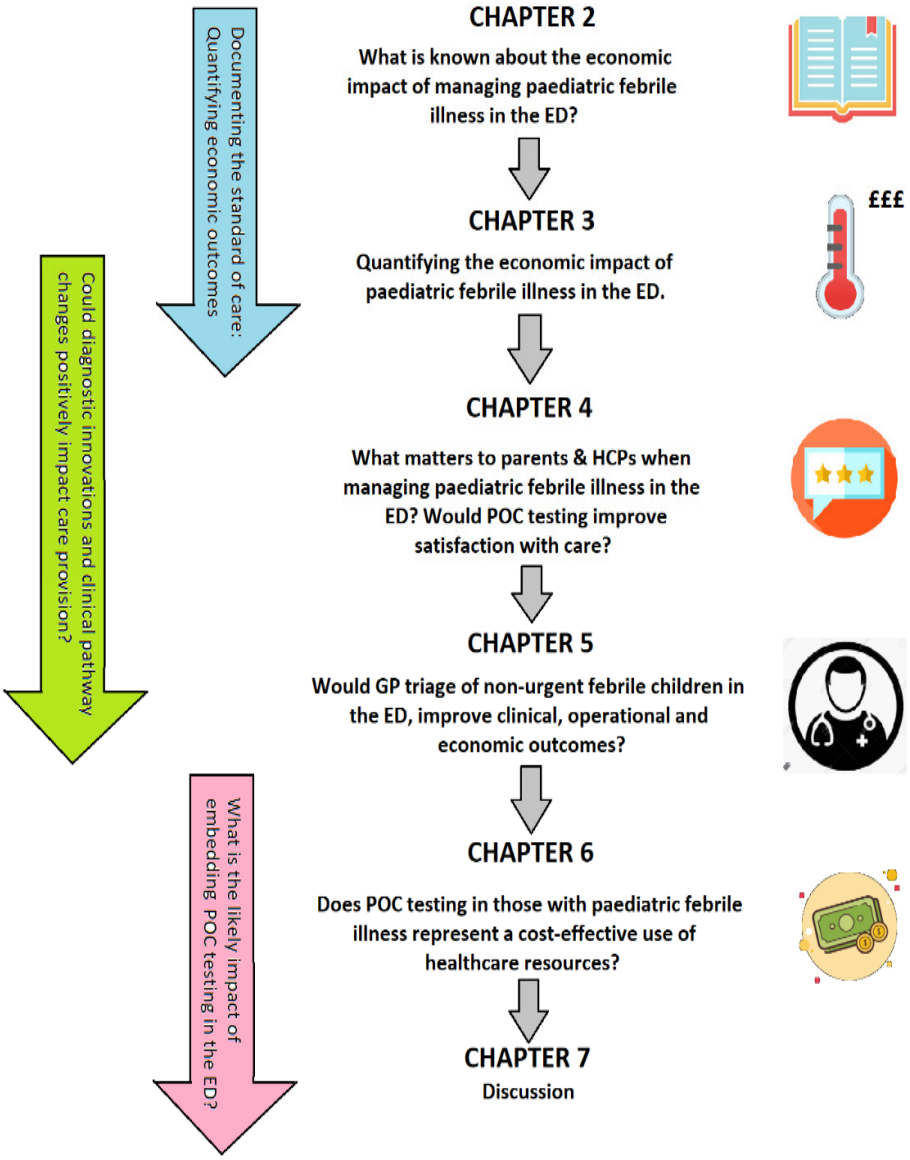
4. GP-led care for non-urgent or low-acuity conditions is becoming increasingly common in EDs. Given that many children with febrile illness are likely to be within this group, how does GP-management of febrile illness impact clinical, economic and operational outcomes compared to ED (specialist management)?

5. Taking everything above into account, could POC-testing for infectious diseases contribute to a more value-based use of scarce NHS resources when managing paediatric febrile illness in the ED for patients and healthcare providers? What are the factors that influence the value of POC testing most?

Structure of the thesis

Figure 2 provides a schematic overview of the studies within the thesis.

Figure 2: Structure of the thesis



Chapter 2: Literature Review – the economic impact of managing paediatric febrile illness in ED settings

Abstract

Background Fever is a common cause of presentation to paediatric EDs, however the aetiology of fever among children is diverse. Underlying viral and bacterial infections can result in almost identical clinical presentations in paediatric patients, making the management of febrile children a clinical conundrum. While additional diagnostic tests can often attribute a cause and site of infection, there is usually at least a couple of hours delay in receiving full blood count and CRP, urine dipstick and microscopy results. Additionally, blood and urine culture results have a 12 to 48-hour turnaround time, thus resulting in delays in clinical decision making. At present, the risk of serious bacterial infection is often too high to ignore, yet too low to justify hospital admission. As such, a 'better safe than sorry' approach is often applied, requiring the employment of scarce resources, antibiotics, and staff time already in high demand, in a patient group who will often be suffering from self-limiting viral infections.

Materials & Methods A comprehensive search of published literature was performed to identify studies examining the healthcare cost implications of the management of febrile infants (temp ≥ 38C) in an ED setting. The search was conducted in MEDLINE (from inception to March 2017), the NHS Economic Evaluation Database (NHSEED), the Cochrane Database of Abstracts of Reviews of Effects (DARE), the National

Institute for Health Research Health Technology Assessment (HTA) database, and the National Institute for Health and Care Excellence (NICE). While the initial literature review, which informed evidence gaps for this thesis was conducted in 2017, the review was updated at the time of writing this thesis in 2020. The primary outcome was the 'overall' cost of management from a health service perspective with secondary outcomes including identification of constituent costs, including medical management, staff time and laboratory investigations.

Results The search resulted in 270 potentially relevant studies. Of these, just six met the inclusion criteria of the review. Included studies were performed between 1993 and 2015, and included data for 10,927 febrile infants, with an age range of 1 day to 6 years, and an average age of 45 days to 1.2 years. Almost all studies were conducted in the United States (n=5), with the exception of one multi-country meta-analysis of patient-level data. The costs reported in the included studies displayed considerable variation. Those reporting healthcare costs for confirmed/suspected SBIs, ranged from £3,533 to £8,648, while children with suspected/confirmed acute respiratory tract infections (ARIs) ranged from £285 to £612 per patient, and those with FWS ranging from £167 to £589 per patient seen (all prices converted to GBP). None of the studies included provided a break-down of constituent costs, including those for antibiotics, staff time and laboratory investigations, with each providing just a single 'overall' cost. Nor did any account for differences in costs by 'sub-group'. As such, risk of bias for the studies collected was considered high and the quality of reporting considered low to moderate in most cases.

Interpretation While fever is a common reason for presentation at EDs, the relationship between diagnostic uncertainty, healthcare utilisation and healthcare costs, remains unclear. The small number of studies identified in this review are subject to systemic differences in the costing approach applied, and in the populations under consideration, thereby limiting meaningful inference regarding the current costs of managing paediatric febrile illness in an ED setting. Research is needed, which acknowledges not only the 'overall' cost per patient seen, but also the relative contributions of constituents, including antibiotics, clinical time, and laboratory investigations; in addition to accounting for differences in management costs for sub-groups of patients, including by age, and working diagnosis. Until such research is available, it is largely unclear what the financial benefits of improving the efficiency and management of fever in the ED, whether through POC tests, risk stratification scores or other markers, will be.

Background

While fever is a common reason for presentation at paediatric EDs (Limper, et al. 2011) (Sands, et al. 2012) the relationship between diagnostic uncertainty, healthcare utilisation and healthcare costs, remains unclear. The implications of failing to identify serious, albeit rare bacterial infections (Van den Bruel, Aertgeerts, et al. 2007), such as meningococcal disease, are clear. Associated adverse outcomes, including neurological impairments, deafness, and amputation (Viner, et al. 2012), impose considerable reductions in either, or sometimes both, quality-of-life (Syngal and Giuliano 2018) and survival, while at the same time, impacting on the quality-of-life

of parents and carers additionally. Aside from the human costs of failing to identify and promptly treat serious bacterial infections before serious and potentially life-changing harms can occur, there are also economic costs to be considered (Bell, et al. 2015). These costs, associated with a lifetime of care for children in whom serious bacterial infections have not been identified or managed optimally can be significant. Although not accounting for the survival, health-related quality-of-life, and caregiver impact, a recent study suggested an estimated £1.3million cost of care over an 'average' lifetime for a survivor of severe meningococcal disease (Wright, Wordsworth and Glennie 2013).

However, utilising a 'cautious-stepped' approach to managing paediatric febrile illness is also not without costs, as this approach requires the use of scarce healthcare resources, which are already in high demand; not just in EDs but across entire health systems. A key tenet of value-based medicine is to ensure that the clinical benefits of additional healthcare spending can justify the costs, particularly when considering the many potential 'other' uses of scarce NHS resources. In the event that this prerequisite is not met, an opportunity cost is incurred, whereby the health generated from additional spending is less than the health that may have been generated if the same resources were used elsewhere in the health system. As a result, the widescale 'overtreatment' and over-investigation of these children, in whom the majority will be suffering from clinically benign viral illnesses (Animut, et al. 2009) (Colvin, et al. 2012), may result in a cost to the health service which outweighs the occasional and infrequent costs associated with failing to identify serious bacterial infections.

The implications to healthcare systems of both under-treating and over-treating children with fever are clearly significant, yet there is currently little room to address the balance. The aim of this literature review is to gather and critically appraise the entirety of published knowledge concerning healthcare costs attributable to managing and treating paediatric febrile illness in an ED setting. The review will aim to discover the key determinants of healthcare resource utilisation when managing fever among children. A key component will be the disaggregation of resource use, whether staff time, antibiotics, or laboratory investigations, in addition to determining differences in the costs of management for various clinical presentations, including FWS, and those with clear viral or bacterial foci. In doing so, it should be possible to begin to build a picture of what the burden of illness associated with the management of paediatric febrile illness is. As a result, it should become clearer what the potential 'value' of improved diagnostic modalities, and reducing the extent of diagnostic uncertainty, is likely to be.

Materials & Methods

Search Strategy

A comprehensive search of published literature was performed to identify papers examining the healthcare resource implications of the management of febrile illness in an ED setting. To be included within the review, studies had to report on the management of children with confirmed fever (≥ 38C) at presentation to the ED (WHO 2018), or children who were apyrexial at presentation, but with a history of fever (≥ 38C) within the three days prior to presentation.

Because resource utilisation and the subsequent costs of managing fever in children are likely to be affected significantly by concomitant illness, including febrile neutropenia secondary to malignancy in the case of febrile illness, this review was limited to studies conducted in children presenting with fever, who were considered 'otherwise well'.

Additionally, the availability and use of different therapeutic options and management strategies for febrile illness, whether novel, established or otherwise, are largely dependent upon the funding available for healthcare provision. As a result, this review was also limited to studies conducted within developed health economies as defined by the United Nations (UN 2014), to minimise the opportunity for discordance and heterogeneity where possible. Relevant studies were identified through a comprehensive literature search in MEDLINE (from inception to March 2017, the NHS Economic Evaluation Database (NHSEED), the Cochrane Database of Abstracts of Reviews of Effects (DARE), the National Institute for Health Research Health Technology Assessment database (HTA), and the National Institute for Health and Care Excellence (NICE). All search terms are provided in Table 1 below. The reference lists of all studies that met the inclusion criteria were hand-searched to maximise retrieval.

Table 1: MEDLINE Search Strategy

MEDLINE Search: Searched 27th December 2017			
1	Febrile	**28**	ED
2	Pyrexial	**29**	Emergency services
3	Pyrexic	**30**	Emergency unit
4	Raised temperature	**31**	Accident and emergency
5	Fever	**32**	Accident & emergency
6	Feverish	**33**	Emergency room
7	High temperature	**34**	ER
8	Pyrexia	**35**	***OR/ 27-34***
9	Hyperthermia	**36**	Economic
10	***OR/ 1-10***	**37**	Cost
11	Paediatric	**38**	Costing
12	Pediatric	**39**	Finance
13	Children	**40**	Financial
14	Child	**41**	Resource
15	Neonate	**42**	Budget
16	Neonatal	**43**	GBP
17	Perinate	**44**	USD
18	Perinatal	**45**	£
19	Infant	**46**	$
20	Toddler	**47**	Dollar
21	Adolescent	**48**	Pound
22	Baby	**49**	Euro
23	Babies	**50**	Burden of illness
24	Teenager	**51**	Health technology assessment

25	Teenage	**52**	HTA
26	***OR/ 11-25***	**53**	***OR/ 36-52***
27	Emergency department	**54**	***AND/ 10, 26, 35, 53***

Selection of studies

All studies identified were screened based solely on their title and abstract in the first instance. Subsequently, for any studies that were not excluded at this point, full text copies were obtained and reviewed against the inclusion and exclusion criteria listed below.

Inclusion criteria

- Population: Studies of otherwise well febrile children aged 16 years or under, presenting to the ED with a temperature of $\geq 38^{o}C$ (rectal, axillary, oral, or tympanic), or a history of fever within the last three days.
- Intervention: Treatment-as-usual, natural history, any interventions indicated for the management of febrile children
- Comparator: Any
- Outcomes: Cost of ED visit (per child), encompassing either/all of diagnosis, laboratory tests, medical management, and staff time.
- Study design: Randomised controlled trials (RCTs) or controlled trials. Observational studies (prospective and retrospective). Economic evaluations and health technology assessments, systematic reviews and meta-analyses.

Exclusion criteria

- Studies with a focus on oncology patients or those suffering from other concomitant disease who may be at increased risk of fever.
- Single case reports
- Studies reporting in non-English language
- Studies conducted in those aged > 16 years
- Studies in which the separation of data for children with fever from other conditions was not possible
- Studies performed in lesser developed countries (UN 2014)

Data extraction

The following data were extracted into a pre-designed data collection form in Microsoft® Excel (Microsoft®, Redmond, WA):

- Author names
- Study title
- Publication year
- Year/s of data collection
- Age range of participants
- Average age of participants,
- Number of participants in the study
- The medical condition under examination in the study (FWS, suspected meningitis etc.)

- The country of origin of the study
- Whether studies included the costs of all participants, not solely those shown later to be positive for a specific condition
- The total cost (per child) of diagnosis and management of febrile illness in the ED

Once collected all cost data were converted to Great British Pounds (GBP £) and inflated to 2019/2020 costs using the consumer price index (CPI).

Risk of bias & quality appraisal

A risk of bias assessment was performed for all included studies. Although the Cochrane risk of bias tool (ROB-2) is popular and recommended in most instances for the evaluation of risk of bias, given the nature of many economic evaluations it was deemed that this would not fit well with economic evaluations. As such, following recommendations of the Cochrane collaboration we chose the Consensus Health Economic Criteria (CHEC), extended checklist, which is an extension of the original CHEC checklist (Evers, et al. 2005) to include a question regarding model-based economic evaluations (Wijnen, et al. 2016). The development of the CHEC-list is based on expert consensus, similar to the development of a Delphi list for quality assessment of randomised controlled trials. Based on several search strategies an initial item pool was developed in which items from existing criteria/check lists were included. Overall, the items included in the CHEC-list are those on which the majority of the expert panel agreed. A benefit of the CHEC-list is that it provides an

insight into the quality of the study performed rather than focusing predominantly on how the study is performed. This tool, along with the BMJ checklist (Drummond and Jefferson 1996) are commonly considered to have more scrutiny than most other lists for the assessment of risk of bias in economic evaluations (Wijnen, et al. 2016).

Results

Details of studies retrieved

The search retrieved 269 potentially relevant studies, 112 from MEDLINE, 1 from NICE, and 156 from the Cochrane DARE, NHSEED and the NIHR Health Technology Assessment (HTA) database, collectively. Four duplicates were removed, with one additional text identified in the reference list of a systematic review (Doan, et al. 2014). This resulted in a total of 266 titles and abstracts to scan, 162 of which did not meet the inclusion criteria at this point, with the remaining 104 subject to full text retrieval. Of these, just six studies met the inclusion criteria of the review and were subsequently included for assessment, as shown in Figure 3. The included studies were performed between 1993 and 2015, and included data for 10,927 febrile infants, with an age range of 1 day to 6 years, and an average age of 45 days to 1.2 years. Most studies were conducted in the United States (n=5) (Hoberman, et al. 1999) (Henrickson, Kuhn and Savatski 1994) (Iyer, et al. 2006) (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (D. Schriger, L. Baraff, et al. 2000), except for one multi-country meta-analysis of patient-level data (Bell, et al. 2015). Details of the studies included are reported in Table 2.

Figure 3: Results of review of published studies

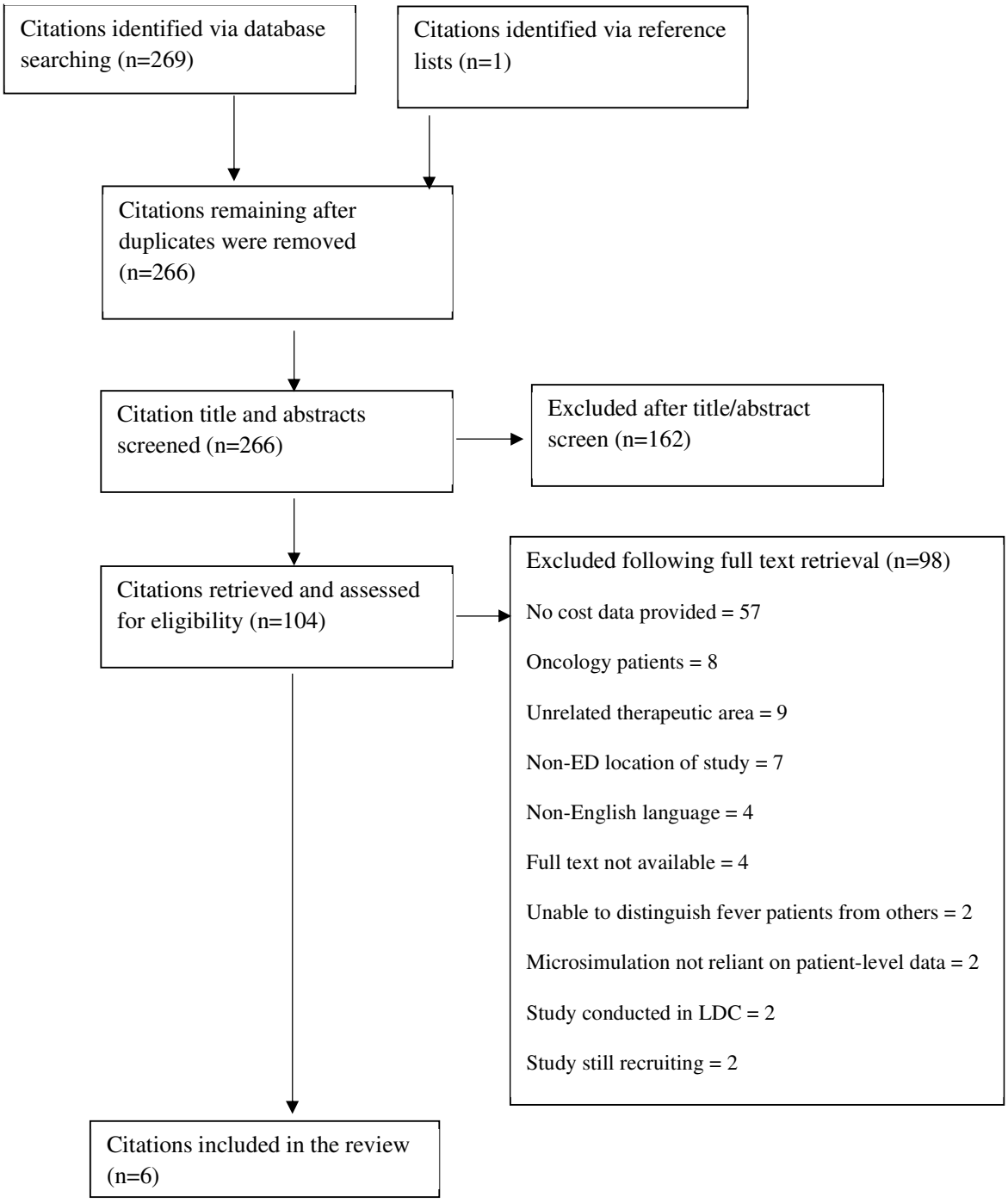


Table 2: Details of included studies

Author	Year	Data from	N	Age	Average age	Country	Study type	Inclusion criteria	Total cost (Converted/inflated)
Bell et al.	2015	2000-2011	881	1month to 16 years	N/A	N/A	Meta-analysis of patient level data	Fever without source (suspected meningitis)	£3,533
Byington et al.	2012	2004-2009	8,431	1 to 90 days	45 days	USA	Observational	Well appearing febrile infants	£167
Iyer et al.	2006	2003-2004	700	2-24 months	11.5 months	USA	Prospective quasi-randomised controlled trial	All febrile children presenting during an influenza outbreak	£612
Henrickson et al.	1993	1989	45	<6 years	N/A	USA	Prospective study	All children with symptoms of LRTI and fever	£354 (HPIV-1), £285 (HPIV-2)
Schriger et al	2000	1992-1995	830	< 3 years	1.2 years	USA	Off-on-off interrupted time series	All children with fever	£589
Hoberman et al.	1999	1999	40	1 to 24 months	8.5 months	USA	Multicenter randomised RCT	Confirmed UTI	£4,253 (Oral therapy), £8,648 (IV therapy)

Risk of bias and quality appraisal of included studies

Table 3 provides details of each included study when assessed against the CHEC-extended item checklist. No single study satisfied all criteria within the assessment, suggesting at least some risk of bias and methodological limitations to consider for each study included. In descending order, the study performed by Bell et al met 11/15 (73.3%) of the relevant criteria, with five criteria omitted as they were not applicable to the study design (Bell, et al. 2015). Hoberman et al. met 11 of 17 relevant criteria (64.7%), the Byington et al. study satisfied 7/15 relevant criteria (46.7%), Henrickson et al. satisfied 6/15 (40%), Iyer et al. met 7/18 (38.9%), and Schriger et al. satisfied 4/17 criteria (23.5%). As shown in Figure 4, most studies did not provide an economic study design appropriate to address the stated objective of the study, leading to the potential for limited-scope bias, nor was a relevant time-horizon provided or justified in the majority of studies. Similarly an assessment of the incremental cost-effectiveness of one intervention or care pathway compared to another, was often not performed, and both sensitivity analyses and discussion around the generalisability of findings were often omitted from the included studies.

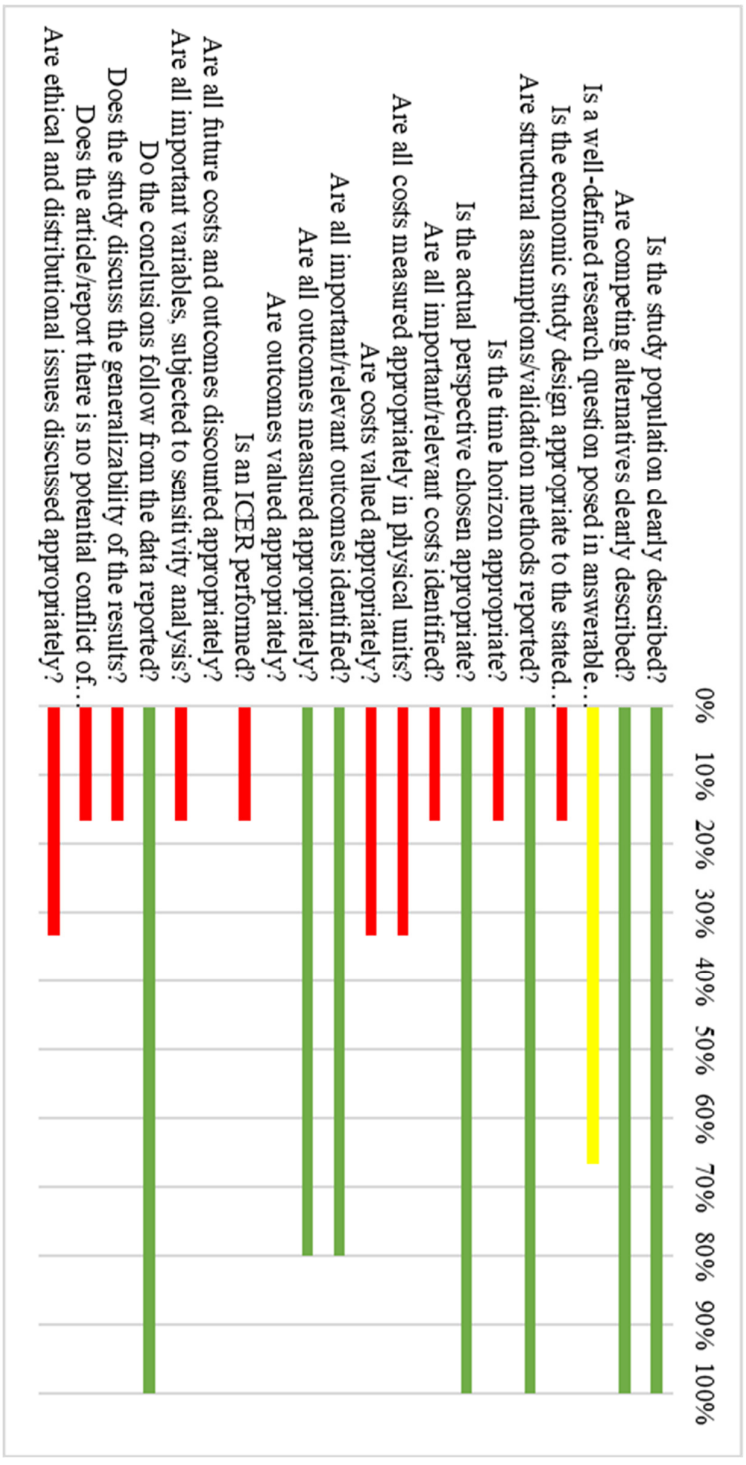
Table 3: Quality appraisal & risk of bias assessment of included studies

CHEC-extended items	Byington et al.	Henrickson et al.	Hoberman et al.	Iyer et al.	Schriger et al.	Bell et al.
Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Are competing alternatives clearly described?	N/A	N/A	Yes	Yes	N/A	N/A
Is a well-defined research question posed in answerable form?	No	Yes	No	Yes	Yes	Yes

Is the economic study design appropriate to the stated objective?	No	No	Yes	No	No	No
Are the structural assumptions and the validation methods of the model properly reported?	N/A	N/A	N/A	N/A	N/A	Yes
Is the chosen time horizon appropriate in order to include relevant costs and consequences?	No	No	No	No	No	Yes
Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant costs for each alternative identified?	No	No	Yes	No	No	No
Are all costs measured appropriately in physical units?	No	No	Yes	No	No	Yes
Are costs valued appropriately?	Yes	No	No	No	No	Yes
Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes	Yes	No	N/A
Are all outcomes measured appropriately?	Yes	Yes	Yes	Yes	No	N/A
Are outcomes valued appropriately?	N/A	N/A	N/A	N/A	N/A	N/A
Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	N/A	N/A	No	No	No	Yes
Are all future costs and outcomes	N/A	N/A	N/A	No	No	N/A

discounted appropriately?						
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	No	No	No	No	No	Yes
Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes	Yes
Does the study discuss the generalizability of the results to other settings and patient/client groups?	No	No	Yes	No	No	No
Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No	No	No	No	No	Yes
Are ethical and distributional issues discussed appropriately?	Yes	No	Yes	No	No	No

Figure 4: Collective quality appraisal of included studies



Approach to estimating the cost of managing paediatric febrile illness in ED settings

Methodological approaches to estimating the economic impact of paediatric febrile illness differed considerably among the studies included in the review. Healthcare costs associated with laboratory testing were included in most (5/6) studies (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (D. Schriger, L. Baraff, et al. 2000) (Hoberman, et al. 1999) (Henrickson, Kuhn and Savatski 1994) (Bell, et al. 2015) as were medicinal costs (4/7) including antibiotics and anti-pyretics (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (D. Schriger, L. Baraff, et al. 2000) (Hoberman, et al. 1999). Three studies included the costs of staff time dedicated to caring for febrile children (Hoberman, et al. 1999) (D. Schriger, L. Baraff, et al. 2000), however no study included both nursing and clinician costs. Similarly, resource use attributable to inpatient admission (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (Iyer, et al. 2006), facilities management (D. Schriger, L. Baraff, et al. 2000) and radiography (Henrickson, Kuhn and Savatski 1994) were only available for a small number of the studies identified. Only one study included the costs of follow up and re-admission (Bell, et al. 2015). Approaches to handling uncertainty and patient heterogeneity were also absent from the majority of studies identified. No study differentiated results by sub-groups of patients, including age, diagnosis, and clinical urgency; however, one study did perform one-way sensitivity analyses to account for sampling bias (Bell, et al. 2015), while only one study provided measures of uncertainty (Iyer, et al. 2006), including 95% confidence intervals and standard errors around the estimates provided, as demonstrated within Table 4.

Table 4: Differences in study methodologies

	Hoberman et al.	**Henrickson et al.**	**Iyer et al.**	**Byington et al.**	**Schriger et al.**	**Bell et al.**
Cost components included						
Medical staff	Yes	No	No	No	Yes	No
Laboratory costs	Yes	Yes	No	Yes	Yes	Yes
Radiography	No	Yes	No	No	No	No
Medicines	Yes	No	No	Yes	Yes	No
Inpatient	No	No	Yes	Yes	No	No
Facilities management	No	No	No	No	No	No
Follow-up	No	No	No	No	No	No
Approach to accounting for uncertainty						
Sub-group analyses	No	No	No	No	No	No
Measures of uncertainty provided	No	No	Yes	No	No	No
Sensitivity analysis	No	No	No	No	No	Yes

Cost implications of managing paediatric febrile illness in an ED setting

Healthcare costs associated with the management of paediatric febrile illness varied considerably within the studies included, ranging from £167 (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) to £8,648 (Hoberman, et al. 1999). Because paediatric febrile illness encompasses a broad spectrum of symptoms and severity, this difference can be explained by differences in patient age, diagnosis, study origin, and costing methodologies, as demonstrated in Tables 3 and 4.

Serious bacterial infections

Two studies reported costs of managing paediatric febrile illness among those with either confirmed or suspected SBIs, reporting on urinary tract infections (UTIs) (Hoberman, et al. 1999) and meningococcal disease (Bell, et al. 2015), respectively. In the case of suspected meningococcal disease in children presenting with FWS, a

multi-country meta-analysis (Northern Ireland, Canada, Spain, New Zealand and Poland) of data collected from 2000-2011, estimated the cost of management at £3,477 per patient in 2015 (Bell, et al. 2015). The second study examining the costs of 40 confirmed cases of UTI in children aged 1-24 months in the USA (Hoberman, et al. 1999) (average age of 8.5 months), reported costs of £4,253 (oral administration of antibiotics), and £8,648 (intravenous administration of antibiotics). However, without clarification as to the frequency of use for each method, it is unclear which estimate is most representative of the current standard-of-care for this facility.

Respiratory tract infections

Two studies included information for those presenting with suspected or confirmed acute respiratory tract infections (ARIs). These studies, both conducted in the USA, were conducted in those aged 2-24 months (Iyer, et al. 2006) and <6 years (Henrickson, Kuhn and Savatski 1994), respectively. One study reporting on children with symptoms of LRTI and fever, provided estimates of £354 for the management of those with confirmed parainfluenza (HPIV-1) and £285 for those with parainfluenza (HPIV-2) (Henrickson, Kuhn and Savatski 1994). The second study, conducted in 2006, reported on all children presenting to the ED with fever during an influenza outbreak, providing an estimate of £612 per patient (Iyer, et al. 2006), which related to the costs attributable to antibiotics and laboratory testing only.

Fever of any cause

Two studies reported on children with fever of any cause (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (D. Schriger, L. Baraff, et al. 2000), which may be

considered the most representative of the broad spectrum of cases observed in routine clinical practice. These studies were performed in the USA and UK, with data collected in the years 2000 and 2012, and in children aged <90 days (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) and <3 years (D. Schriger, L. Baraff, et al. 2000) respectively. The study conducted by Byington et al. estimated the costs of managing febrile illness in a US ED at £167 per patient, however this was limited to the costs of laboratory investigations alone. This can therefore be viewed as a likely underestimate of the true burden of managing febrile illness. The second study again in a US ED, provided an estimate of £589, in which only the costs of antibiotics and admission/time in the ED were included (D. Schriger, L. Baraff, et al. 2000).

Discussion

Principal findings

A comprehensive literature review was conducted to assess the healthcare costs associated with the management of paediatric febrile illness, among 'otherwise well' children, in an ED setting. The results of this review clearly highlight the paucity of evidence regarding the 'true' financial impact of paediatric febrile illness in ED settings, with stark variability in reported resource utilisation and subsequent healthcare expenditure. This was exacerbated by considerable differences in study populations and costing methodologies, with several methodological and reporting limitations for each of the studies included. This left considerable opportunity for various sources of bias to impact the findings of the studies. As such, among the small number of studies identified which attempted to estimate the cost of managing

paediatric febrile illness, meaningful comparison and synthesis of findings was difficult.

Just two studies identified in the review (Bell, et al. 2015) (Hoberman, et al. 1999) provided any definitive patient-level data which could account for the costs of the many different points of interaction within paediatric febrile illness management pathways. While these studies collectively accounted for the costs associated with antibiotic administration, diagnostic tests, and subsequent inpatient admission; it was not clear how each element individually contributed, as a proportion, to the 'overall' healthcare cost estimations provided within the studies, with estimates of costs instead provided at the aggregate level.

While two studies utilised a broad, thorough, and inclusive approach to the costing of paediatric febrile patients (Hoberman, et al. 1999) (Bell, et al. 2015), these were performed among study populations with either suspected or confirmed serious bacterial infections, with budget impact in these instances, ranging from £3,477 (Bell, et al. 2015), to £8,648 per patient (Hoberman, et al. 1999). While acute UTIs are common in children, with 8.4% of girls and 1.7% of boys having suffered at least one episode by the age of seven (Hellström, et al. 1991), these are approaching the severe end of the febrile aetiological spectrum. As such, it is therefore likely that these estimates represent an over-estimation of the true costs of managing febrile illness in the 'average' child presenting with fever to the ED.

By restricting attention solely to studies with heterogeneous cohorts, namely 'all febrile children' or 'well appearing febrile children' (D. Schriger, L. Baraff, et al. 2000) (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (Iyer, et al. 2006), which may be considered more representative of the broad spectrum of cases observed in routine clinical practice; the mean cost per patient of managing paediatric febrile illness fell significantly. By limiting attention to studies that costed all patients, and not just those with confirmed viral or bacterial foci for fever, the results of this review suggest a cost of approximately £612 (Iyer, et al. 2006) per patient. It is important to note however, that because the small number of studies identified are non-uniform in their approach to what is costed and what is not, they should be considered indicative at best. As such, the true cost of managing febrile illness in the ED can be expected to fall somewhere between the extremes of £167 in otherwise well febrile infants (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) and £8,648 in cases of serious bacterial infections (Hoberman, et al. 1999). However, as identified by this review, no study to date has been either large enough, representative enough or recent enough, to provide an estimate which may be generalised to the full spectrum of presentations for paediatric febrile illness within modern healthcare systems.

Strengths and weaknesses of the chapter

To the best of the author's knowledge this is the first comparative review of the healthcare cost implications of managing febrile illness in an ED setting, making it a novel addition to the existing evidence base. Additional strengths include the broad perspective applied for the inclusion of studies. RCTs, while useful for measuring clinical efficacy, often do not provide the most accurate reflection of real-world

clinical practice (Booth and Tannock 2014). This is in part due to restrictive and often unrepresentative inclusion criteria, in addition to reporting biases, and systemic differences in care practices that arise from being part of an RCT. As such, the subsequent costs reported in these studies can often be misleading and misrepresentative of the costs associated with routine clinical practice, where study protocols are not strictly adhered to. Through the inclusion of observational data, the external validity of this study has therefore likely been increased as a result.

Nonetheless, though broad inclusion criteria can be considered a strength when anticipating a relatively minimal evidence base, as observed within this review, the same can also be considered a weakness. The diverse age ranges under consideration within the included studies (from one day to 16 years), in addition to the wide time interval between studies included (1993-2015), may have led to imprecision in the findings of the review. It can be expected that over time, attitudes, knowledge, and the subsequent management of a condition will change, usually for the better as evidence grows and transformational change is gradually implemented. This includes, but is not limited to access to improved technologies and care processes, including vaccination (Koshy, et al. 2010), or the management of related conditions including tonsillectomy for the management of tonsillitis (Koshy, Murray, et al. 2012) which can dramatically change the landscape of presentation to the ED. As such, audits of clinical processes and resulting budget impact estimates made in one year, may not always be comparable with those made in another, owing to the significant potential for changes in what is considered 'best practice'. Furthermore, increasing demand for ED services year on year (Gill, et al. 2013), leave the possibility that conditions experienced during

a given study period, and the factors driving decision making as a result, including staffing levels and short stay capacity are not comparable. This means that comparisons of one study estimate under a specific set of conditions in a given year, are difficult to compare and synthesise with others collected under different circumstances, a problem not unique, but common within emergency care, given increasing demands for services (Cecil, et al. 2015). As a result, this study could perhaps have benefitted from a narrower study inclusion period. While this would have undoubtedly limited the retrieval of studies in an area already suffering from a paucity of published studies, this would have likely provided more accurate evidence, minimising the possibility for heterogeneity being a primary driver of differences in the observed costs per febrile patient managed in the ED. Additionally, the strong over-representation of studies from the United States (5/6), raises questions regarding the validity of this evidence in an EU, UK, or more broadly, public as opposed to privately funded healthcare system context. It is well known that healthcare costs under private insurance systems are subject to market forces, resulting in increased costs of healthcare (OECD 2015), and as such, the validity of such estimates to other healthcare systems is unclear. Similarly, our use of the consumer price index to inflate healthcare costs from studies published over a twenty-year time frame, may also represent a limitation. While the use of the CPI to provide a net present value is common within academic research and health research more specifically, other alternatives may have been used which more accurately reflect how inflation impacts prices within healthcare settings. Use of the Hospital and Community Health Services (HCHS) Index may have led to a more accurate representation of present day costs,

and therefore without a comparison of how each compared against one another, this should be considered as a limitation.

Finally, by focusing the chapter exclusively on the healthcare systems costs associated with the management of paediatric febrile illness in ED-settings, the findings of this chapter have missed two key considerations, those of parental and child quality-of-life and survival. In the event of serious sequelae following SBIs, it is not only healthcare costs which must be considered but also the opportunity cost of forgone potential healthy years lived, and the impact caring for a child may have on parental quality-of-life. While not the remit of this chapter, this is a clear limitation when interpreting the findings presented as they address only a proportion of the true costs of managing paediatric febrile illness.

Implications for future research

This literature review was originally performed with data up to March 2017, in May 2020 an update of the review was conducted. While four additional studies were identified, only one met the inclusion criteria of the literature review. This study is presented in the next chapter of this thesis, which was designed to fill the evidence gap that this initial review identified. With a lack of definitive evidence, future research should aim to address the current lack of budget impact evidence regarding the management of paediatric febrile illness, from an EU perspective. Furthermore, owing to the variable and generally limited reporting of constituent costs, significant

utility could be obtained from future studies which address not only how much antibiotics, staff time and laboratory investigations account for as a proportion of total costs, but also examine how these costs may differ with respect to different patient sub-groups. Each study identified within the review provided no indication regarding how the costs of managing febrile illness may differ with respect to observable patient characteristics, despite evidence suggesting that resource utilisation in general is positively associated with children under 2 years of age (Berry, et al. 2008). Additional research which considers not only the financial impact of paediatric febrile illness, but also the quality-of-life impact of both short-term and long-term associated symptoms and conditions may also provide significant benefit. In a time of rapid innovation for ED diagnostics, and particularly with respect to the management of infectious diseases, significant value could be realised from research which provides a credible 'base-line' from which to improve upon.

Chapter 2 summary

While fever is a common reason for presentation at paediatric EDs, the relationship between diagnostic uncertainty, healthcare utilisation and healthcare costs, remains unclear. A small number of studies were identified; however, these were characterised by significant heterogeneity, with highly variable data collection periods, settings, costing methodologies and inclusion criteria. Additionally, the evidence provided was conducted, in the majority, 20 years ago, with over 80% of published works originating from the United States. Additional research is therefore required in order to clarify the current resource use, and economic costs attributable to the management

of paediatric febrile illness in ED settings in the UK. Furthermore, this evidence should acknowledge not only the 'overall' cost per patient seen, but also the relative contribution of constituent costs, including antibiotics, clinical time, and laboratory investigations. Incorporation of a representative sample of children will be key to understanding what contributes to the budget impact of managing paediatric febrile illness in ED settings, as currently, only a single study has included children of varying aetiologies of febrile illness, which therefore approximate a real-world clinical setting. The aim of the following chapter will be to empirically assess the real-world economic impact of paediatric febrile illness in ED-settings and aim to fill this gap in the literature. In doing so, it should be apparent what the financial benefits of improving the efficiency and management of fever in the ED may be, whether through POC tests, risk stratification scores, or other markers.

Chapter 3: The cost of diagnostic uncertainty: A prospective observational analysis of 6,518 febrile children attending the ED over a one-year period.

Abstract

Background Paediatric fever is a common cause of ED attendance. A lack of prompt and definitive diagnostics makes it difficult to distinguish viral from potentially life-threatening bacterial causes, necessitating a cautious approach. This may result in extended periods of observation, additional radiography, and the precautionary use of antibiotics (ABs) to deal with bacterial foci. This study examines resource use, service costs, and health outcomes among children presenting to the ED with fever.

Methods We studied an all-year prospective, comprehensive, and representative cohort of 6,518 febrile children (aged <16 years), attending Alder Hey Children's NHS Foundation Trust, an NHS-affiliated paediatric care provider in the North West of England, over a one-year period. Performing a time-driven and activity-based costing (TDABC), this chapter estimates the economic impact of managing paediatric febrile illness, with a focus on nurse/clinician time, investigations, radiography and inpatient stay. Using bootstrapped generalized linear regression modelling (GLM, gamma, log), we identified the patient and healthcare provider characteristics associated with increased resource use, applying retrospective case-note identification to determine rates of potentially avoidable antibiotic prescribing.

Results Infants aged less than three months incurred significantly higher resource use than any other age-group, at £1000.28 [95% CI £82.39 - £2,993.37] per child, ($p<0.001$); while lesser experienced doctors exhibited 3.2-fold [95% CI 2.0 - 5.1-fold] higher resource use than consultants, ($p<0.001$). Approximately 32.4% of febrile children received antibiotics and 7.1% were diagnosed with bacterial infections. Children with viral illnesses for whom antibiotic prescription was potentially avoidable incurred 9.9-fold [95%CI 6.5-13.2-fold] cost increases compared to those not receiving antibiotics, equal to an additional £1,352.10 per child; predominantly resulting from a 53.9-hour increase in observation and inpatient stay (57.1 vs. 3.2 hours). Bootstrapped GLM suggested that infants aged below three months, those prompting a National Institute for Health and Care Excellence (NICE) respiratory rate "red flag", treatment by lesser-experienced doctors and those triaged as Manchester Triage System (MTS) yellow or higher, were statistically significant predictors of higher resource use in 100% of bootstrap simulations.

Interpretation The economic impact of diagnostic uncertainty when managing paediatric febrile illness is significant, and the precautionary use of antibiotics is strongly associated with increased costs. The use of ED resources is highest among infants (aged less-than-three months), and those infants managed by lesser experienced doctors, independent of clinical severity. Diagnostic advances which could increase confidence to withhold antibiotics, may yield considerable efficiency gains in these groups; where the perceived risks of failing to identify potentially life-threatening bacterial infections are greatest.

Background

As demonstrated within the previous chapter, while fever is a common reason for presentation at paediatric EDs (Alpern and Henretig 2006) (Van den Bruel and Thompson 2014), the relationship between diagnostic uncertainty, healthcare utilisation and healthcare costs remains unclear. A lack of empirical studies assessing the budgetary and resource impact of managing this highly common condition means that the economic implications of having to choose between the potential over-treatment of febrile children on the one-hand, and the prospect of failing to identify potentially life-threatening SBIs on the other, is also unclear. While the literature review presented in the previous chapter of this thesis revealed a handful of studies examining the healthcare implications of managing febrile illness; these were characterised by significant variability, limited not just to clinical settings and study dates, but also with respect to the inclusion criteria and costing methodologies employed. This highly differential approach to estimating costs, which is not solely a phenomenon with ED-based economic evaluations (Mercier and Naro 2014) (Cunnama, et al. 2016) (Burgess, et al. 2020), while common, nevertheless undermines our understanding of the impact of managing paediatric febrile illness in real-world settings. The result is that no common approach to measuring resource use and economic costs attributable to managing paediatric febrile illness in the ED, has been achieved.

As a result, it is difficult, based on existing literature, to assess the true, real-world impact of managing paediatric febrile illness in ED-settings, and particularly so within the UK, with the majority of studies to date published in US settings where payment

structures vary significantly from those observed under the NHS. The aim of this chapter is therefore to clarify current resource use, and economic costs attributable to the management of paediatric febrile illness in ED settings, acknowledging not only the 'overall' cost per patient seen, but also the relative contribution of constituent costs; including antibiotics, clinical time, and laboratory investigations. Exploration of drivers of costs, whether patient-centric, including age, diagnosis, or MTS triage classification, or HCP-centric, including years of experience and clinical role, will also supplement our understanding of drivers behind the costs of managing paediatric febrile illness. This in turn should for the first time, provide a baseline assessment of what the 'value' of changing diagnostic processes for the management of paediatric febrile illness may be. Using a bottom-up TDABC, the aims of this chapter are therefore to: (1) estimate the economic impact of managing febrile illness episodes in children of all ages and presenting complaints, in an NHS paediatric ED setting, (2) to identify how management practices and costs vary with factors including patient age, and the experience of treating clinicians, and, (3) to provide insights regarding where any diagnostic advances currently under development, including molecular diagnostics, protein biomarkers, and POC testing technologies, are likely to yield the greatest clinical and socioeconomic value, by reducing clinical uncertainty increasing confidence to withhold antibiotics. This chapter of this thesis was published in BMC Medicine on March 6th 2019 (Leigh, Grant, et al. 2018).

Materials & Methods

Participants & Methods

This study applies TDABC, a bottom-up approach to healthcare costing, which maps pathways observed during routine clinical practice, identifies all points and durations of interaction therein, and assigns time-dependent costs to each constituent. The costs of non-time-dependent activities, including tariff-based ancillary investigations, are subsequently added to provide a representative activity-weighted cost per completed treatment episode. While time-consuming compared to established costing methodologies including reference costing, this approach, which is most often applied to the appraisal of surgical interventions (Palsis, et al. 2018) (Pathak, et al. 2019) (Akhavan, Ward and Bozic 2016) has grown in popularity within paediatric research (Nguyen, et al. 2020) (Caloway, et al. 2020) (Crocker-Buque, et al. 2019), demonstrating more accurate reflections of costs when compared to conventional methods which rely predominantly on reference costing (Akhavan, Ward and Bozic 2016) (Simmonds, et al. 2019). However, no studies to date have applied this methodology in an ED setting.

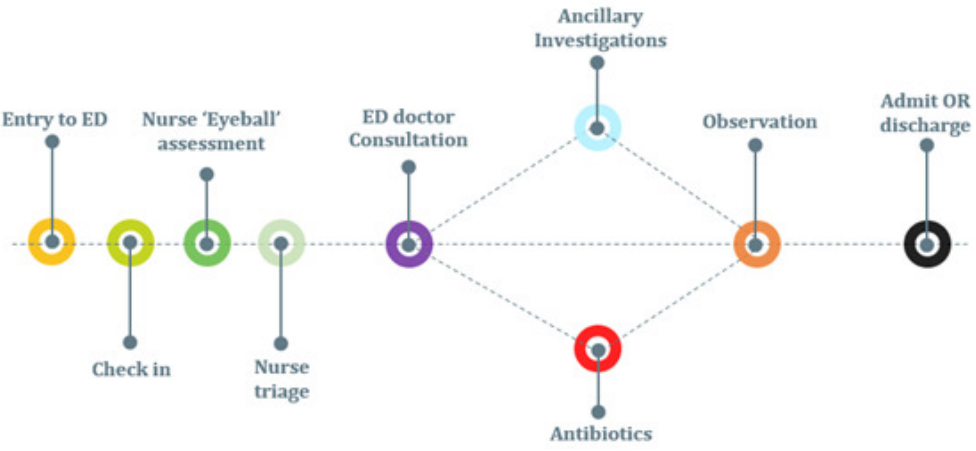
A total of 8,552 consecutive febrile children, with a temperature above 38ºC at presentation, or below 38ºC with an unverified parent-reported history of fever up to 3 days previous, were prospectively identified. All children visited Alder Hey Children's NHS Foundation Trust, a large paediatric specialist care provider in the North West of England, between 1st September 2012 and 31st August 2013. Children were excluded if: (1) data concerning key components of their stay, including the treatments provided, or healthcare personnel seen, were missing or incomplete, or (2)

if there were pre-existing medical conditions likely to modify ED care pathways from those of the average 'otherwise well' patient, including paediatric oncology patients.

A schematic of the clinical pathway used for this study is provided in Figure 5. Children were initially seen by a qualified ED nurse who conducted an initial evaluation, using the MTS (Zachariasse, et al. 2017). MTS assessments follow a flow chart based on the patient's reason for contacting the ED. The chart begins by identifying possible criteria indicating life-threatening conditions for the patient, and if none of these conditions are present, the nurse continues along the flow chart asking questions until the nurse assigns the patient an appropriate category. The nurse's experience can contribute to the assessment, but on the other hand, the risk of the nurse missing serious conditions is reduced because the flow chart forces the nurse to ask key questions and make vital inquiries. Children were triaged as green 'standard', yellow 'urgent', orange 'very urgent' or red 'immediate attention'. For several children, borderline 'yellow/red' or 'orange/red' categories were applied. This was a result of uncertainty during triage, and such children had their MTS classification amended with increased or reduced urgency following a second opinion with a nurse or clinician. Diagnostic categories, defined as: (1) definite bacterial, probable bacterial or bacterial syndrome with low/no inflammatory markers, (2) definite viral, probable viral, or viral syndrome with no/high inflammatory markers, (3) trivial illness, (4) inflammatory illness, and (5) unknown/insufficient information, were applied retrospectively, based on an adapted algorithm from Herberg et al (Herberg, et al. 2016). In any instance where uncertainty or disagreement occurred regarding the appropriate classification, these cases were marked and decided upon by two

consultants specializing in paediatric infectious disease. All cases had notes including CRP, neutrophils and sterile site pathogenic bacteria recorded such that diagnosis classifications could be quality checked to ensure consistency. For this analysis, definite bacterial, probable bacterial and bacterial syndromes with low/no inflammatory markers, were collectively defined as 'bacterial aetiologies', while definite viral, probable viral, and viral syndromes with no/high inflammatory markers were collectively defined as 'viral aetiologies'. As with similar studies (Elfving, et al. 2016), the prescription of antibiotics for patients with anything other than a bacterial aetiology of fever, was for this study, defined retrospectively as "potentially avoidable".

Figure 5: Clinical pathway of paediatric febrile illness used for patient-level costing



Because time stamps documenting the duration of contact with healthcare personnel for various treatments and investigations are not routinely collected as part of NHS electronic patient records, these were imputed in one of two ways. Firstly, estimates

were provided by staff actively involved in the provision of ED care. Secondly, prospective time-in-motion data were collected for a representative cohort of 71 febrile children presenting to Alder Hey Children's NHS Foundation Trust ED between January 6th and February 12th, 2017. Four 5th year medical students collected the data by 'shadowing' patients reporting to the book-in desk with fever as a symptom. Additionally, any patients suspected of fever by clinical teams (such as the nurse performing initial visual assessment) were additionally identified. The researchers followed patients through the ED, documenting all points of interaction with HCPs using a stopwatch and a pre-designed case report form. Parental consent was obtained prior to data collection. Data were collected in four hourly blocks during the day (8a.m-4p.m), evening (4p.m-12a.m) and early morning (12a.m-4a.m), seven days a week. For any events which were not observed during implementation of the time-in-motion study, including clerical and administrative tasks such as writing up patient notes, these were estimated following a Delphi panel approach. In all such cases a number of estimates were obtained, and the average time used, because tasks such as inserting a cannula for example, can be expected to take varying lengths of time depending upon factors such as experience, co-operation of the child, state of hydration or vascular filling. All timings used are provided in Table 5.

Table 5: Staff time associated with components of the paediatric fever pathway

ACTIVITY	MEAN DURATION (MINS)
Triage time (Nurse)*	4.5
Clinician consultation time (MTS Green) *	16.2
Clinician consultation time (MTS Yellow) *	19.4
Clinician consultation time (MTS Orange) *	21.1
Clinician consultation time (MTS Red) *	22.7
Clinician time - Writing up patient notes#	10
Order blood/urine culture (Clinician)#	10
Arrange X-ray (Clinician)#	6
Book patient into the ED (Receptionist)#	2
Refer patient to other specialties (Clinician)#	20
Insert cannula (Clinician)*	20
Provide antibiotics/other medicines (Nurse)#	5
Visual assessment triage (Nurse)*	2
Interpret results of ancillary investigations (Clinician)#	10

**Collected during time-in-motion study*

 # Estimate provided by ED consultants

Unit costs

Hourly salaries for healthcare personnel were provided by the patient-level costing department at the Trust. Except for clinicians, salaries for those working either: (1) weekdays between 7pm and 7a.m, or, (2) at the weekend, had their hourly rate increased in line with NHS guidance on working unsocial hours (NHS 2017). Costs for non-time driven activities, including laboratory-based investigations, were

obtained from the Trust's finance department and NHS reference costs 2015/16 (Gov.uk 2016).

Pharmaceuticals were assigned unit costs from the British National Formulary (BNF 2020). As data concerning the precise antibiotics provided to patients were not available, we assumed that antibiotic prescribing was in line with the recommendations provided within NICE CG160 (NICE 2017). Namely, where intravenous (IV) antibiotics were prescribed, both a third-generation cephalosporin (cefotaxime, ceftriaxone) and an anti-listeria agent were provided (amoxicillin, ampicillin) for infants under 1 month, and a third-generation cephalosporin alone if more than 1 month. In cases of empiric IV antibiotic therapy, it was assumed that a third-generation cephalosporin directed against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and *Haemophilus influenzae type b* was provided. Where oral antibiotics were prescribed it was assumed that amoxicillin or cephalexin were provided as per local antimicrobial guidance.

Costs incurred during inpatient stay were obtained from NHS reference costs 2015/16 (Gov.uk 2016). The tariff HRG PW20C (paediatric fever of unknown origin, CC score = 0) was utilised to reflect a three day short stay inpatient admission. As children could be admitted for anywhere between one and 72 hours under the reference tariff, this figure was divided through by 72 and multiplied by the number of hours of inpatient admission recorded for each child. Patients who exceeded the three-day limit incurred an excess bed day charge which was applied from the fourth day until discharge. Finally, indirect costs were estimated for each child using the 'full absorption

approach' (Gupta and Parmar 2001). This included the anticipated use of facilities such as toilets, and the time of administrative staff typing up and sending discharge notes to patient's general practitioners (GPs). Societal costs, including parental absence from work, and children's absence from school were not included, as the analysis was conducted from a healthcare provider perspective. Due to the short time frame of the analysis, costs were not discounted. All unit costs were in 2017 prices and are provided within Table 6.

Table 6: Unit costs by component of paediatric febrile illness pathway

ITEM	UNIT COST
INVESTIGATIONS (PER TEST)	
Amylase	£6.00
Bacterial PCR	£158.00
Bilirubin	£6.00
Biochemistry Profile	£8.00
Blood albumin	£6.00
Blood glucose test	£6.00
Blood Culture	£35.00
Blood gas #	£7.00
Blood taken	£3.00
Calcium profile	£7.00
Clotting screen	£5.00
Creatinine	£6.00
CRP	£6.00
CSF	£6.00

CT scan (Head)	£201.00
ECG	£33.00
ENT Swab	£19.00
ESR	£4.00
FBC	£3.00
Glandular fever screen	£4.00
Group and save	£12.00
LFTs	£7.00
Magnesium	£6.00
Malarial parasites test	£21.00
Measles PCR	£55.00
Meningo pneumo PCR	£25.00
Meningococci screen	£6.00
Mycoplasma SER	£23.00
Pertussis swab	£9.00
Phosphate	£6.00
Rapid Strep Test	£9.00
Renal profile	£46.00
Respiratory PCR	£117.00
RSV screen	£12.00
Ultrasound	£55.00
Urinalysis #	£8.00
Urine albumin	£6.00
Urine culture #	£8.00
Urine dipstick #	£6.00
Urine Sample	£8.53
Virus PCR	£56.00
X-ray	£46.00

ANTIBIOTICS (PER DOSE/COURSE)	
Amoxicillin 125mg (Suspended) *	£1.16
Amoxicillin 125mg (IV) *	£4.34
Amoxicillin 250mg (Susp.) *	£1.33
Cefotaxime 195mg (IV) *	£0.48
Cefotaxime 575mg (IV) *	£0.66
NURSE TIME (PER HOUR)	
Band 5	£15.43
Band 6	£18.95
Band 7	£22.50
Band 8a	£27.39
DOCTOR TIME (PER HOUR)	
FY1/FY2	£24.24
ST1-3	£30.79
APNP	£27.39
Registrar	£39.02
Consultant	£76.11
REFERRAL TO OTHER SPECIALTIES	
Surgery	£178.55
Medicine	£272.74
ENT	£146.92
Neuro	£411.78
INPATIENT ADMISSION	
Short stay (HRG PW20C, 3 days non-elective stay) #	£1,712
Excess bed day charge #	£462

*Unit costs provided by Alder Hey Children's NHS Foundation Trust Finance Team unless otherwise stated # NHS Reference costs 2016 * British National Formulary 2017*

Outcomes & statistical analysis

Summary statistics are provided to describe the characteristics of participants. Categorical variables were summarised by frequency and percentage, while continuous variables were reported as mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum values. The primary outcome was the 'cost per completed febrile illness episode', with an 'episode' defined as the period from booking into the ED to final discharge, enabling the possibility for re-attendances to be included. We additionally performed sub-group analyses to account for patient and healthcare provider heterogeneity. As our primary outcome data were both non-normally distributed, and characterised by sub-groups of unequal size, the Kruskal-Wallis test was applied to assess statistical significance. Dunn's post-hoc pairwise comparison (adjusted by the Holm FWER method), as used in previous studies (Raimondi, et al. 2019) (Reynders, et al. 2020), was used to determine where significant differences were present. Results were reported as p-values and considered statistically significant at the standard 5% level. Multivariate regression analysis using a GLM was performed to estimate conditional mean health expenditure and identify covariates associated with increased healthcare utilisation. Because several prior studies have demonstrated that the gamma family with a log error link is not only robust, but also the most commonly applied approach in healthcare cohorts in which positive and skewed healthcare costs are guaranteed (Hardin and Hilbe 2007)

(Manning, Basu and Mullahy 2003), our analysis also assumed a gamma error distribution with log-link.

Finally, because all timings employed within the TDABC were estimates, and therefore subject to one or more of (1) sampling bias, (2) Hawthorne effects, or (3) reporting bias; a distribution of credible times for each patient interaction with healthcare personnel was used in the TDABC, to reflect the uncertainty inherent to sampling. For all parameters contained within the TDABC, continuous variables (time in consultation with clinician, days spent as inpatient) were randomly sampled from gamma distributions as explained by Briggs (Briggs 2005). Dichotomous variables (percentage of triage assessments performed by band 5/6 nurses) were sampled from representative beta distributions constructed from the sample data available, as explained in previous work by Briggs et al (Briggs, Sculpher and Claxton 2006). For estimates reliant on expert opinion which were not observed during the time-in-motion study due to a low frequency of occurrence, uniform distributions were sampled in absence of information concerning the true sample mean and variance. This approach was taken as in the absence of population estimates, any other type of distribution would have intrinsically imposed assumptions regarding the distribution of true population values. By selecting a uniform distribution in the absence of such evidence, all subsequent draws remained completely random. In choosing this distribution we combined and ranked response data from all HCPs (of varying roles and experience) surveyed, to define lower and upper limits or 'bounding' criterion. Once responses were provided, respondents were informed of responses by other respondents to gauge their belief in the credibility of different responses and ensure that the distributions

utilized were plausible. GLM regression modelling was subsequently replicated for 100 bootstrapped costing datasets randomly utilizing parameter values from all plausible distributions, for all variables; to assess the sensitivity of the primary outcome, the cost per febrile illness episode, and the resulting GLM coefficients, to changes in the values of underlying input parameters. This method has previously been used by Jones et al. (A. Jones 2000). Details of all distributions utilized are provided in Table 7. All analyses were performed using STATA 14 (StataCorp LP, USA) and Microsoft® Excel™, (Redmond, WA).

Table 7: Distributions used for probabilistic sensitivity analysis

PARAMETER	DISTRIBUTION
TIME (HOURS)	
Nurse triage	Gamma (4.69, 0.01)
Proportion performed by band 6 nurses	Beta (16,55)
Proportion performed by band 5 nurses	1- Beta (16,55)
Clinical consultation	Gamma (3.9, 0.04)
Clinician writing up patient notes	Uniform (1,20)
Arrange blood/urine culture	Uniform (1,25)
Arranging X-ray	Uniform (1,30)
Receptionist booking patient in	Uniform (1,5)
Clinician arranging referral	Uniform (1,25)
Clinician cannulating child	Uniform (5,35)
Nurse providing antibiotics to child	Uniform (1,10)

Visual assessment by nurse	Uniform (0.5,5)
Days spent as inpatient (if admitted)	Gamma (3.72, 1.03)
SALARY (COST/HOUR)	
Nurse (band 5)	Uniform (13.36,17.5)
Nurse (band 6)	Uniform (16.14,21.77)
Nurse (band 7)	Uniform (19.34,25.67)
Nurse (band 8a)	Uniform (24.8,29.99)
Foundation year doctor	Uniform (22.5,26)
ST1-3	Uniform (27, 30.8)
APNP	Uniform (24.8,29.99)
Registrar	Uniform (36,41)
Consultant	Uniform (64.8,87.4)

Results

Descriptive statistics

8,552 individual ED attendances were identified over the study period, with 2,034 excluded from the analysis due to incomplete data or failing to meet the inclusion criteria. This resulted in a complete dataset of 6,518 observations (Table 8). Comparison of baseline characteristics indicated that there was no significant difference in observable characteristics between those included and excluded from the analysis; including but not limited to age, final diagnoses, MTS classification and temperature.

Table 8: Descriptive statistics of study participants in TDABC

	MEAN (SD)	MEDIAN (IQR)	MIN	MAX
Age	3.28 (3.09)	2.17 (3.5)	4 days	15.98 years
Gender Male (Freq)	53.5% (3,484)	-	-	-
Temperature	38.7 (1.07)	38.6 (1.7)	35	41.4
Respiratory rate (bpm)	29.95 (9.23)	28 (8)	14	188
Pulse (bpm)	138.7 (25.98)	138 (37)	22	250
MANCHESTER TRIAGE SCALE CLASSIFICATION				
MTS Green (Freq)	47.52% (3,097)	-	-	-
MTS Yellow (Freq)	8.88% (579)	-	-	-
MTS Yellow/Red (Freq)	0.17% (11)			
MTS Orange (Freq)	17.06% (1,112)	-	-	-
MTS Orange/Red (Freq)	23.03% (1,501)			
MTS Red (Freq)	0.39% (27)	-	-	-
MTS Not recorded (Freq)	2.9% (191)	-	-	-
TIMINGS				
Time between booking and triage (mins)	15.3 (14.7)	11 (18)	0	71
<10 mins	47.8%			
11-20 mins	24.1%			
21-40 mins	20%			
41-60 mins	5.6%			
>61 mins	2.5%			
Time between triage and consultation (mins)	67.9 (52)	55 (65)	0	609
<30 mins	26.9%			
31-60 mins	27.7%			
61-120 mins	30.8%			
121-180 mins	11.4%			
181-240 mins	2.6%			
> 240 mins	0.6%			
Time in ED post consultation (mins)	68.4 (70.6)	45 (72)	0	630

<30 mins	43.5%				
30-60 mins	15.1%				
61-120 mins	24.8%				
121-180 mins	9.7%				
>181 mins	7%				
Total time in ED (mins)	151.6 (81.3)	135 (98)	16		729
<60 mins	8.3%				
61-120 mins	32.7%				
121-240 mins	46.9%				
241-360 mins	9.6%				
>361 mins	2.5%				
Inpatient length of stay (Days)					
Not hospitalised	93.51%				
1-3 days	3.42%				
4-7 days	2.43%				
8+ days	0.63%				
Reattendance (Freq)	3.43% (224)	-	-	-	
Afterhours (Freq)	88.9% (5,798)	-	-	-	
Winter (Freq)	60.1% (3,918)	-	-		-
REVIEWING CLINICIAN					
APNP	2.73% (178)	-	-		-
Consultant	7.99% (521)	-	-		-
Foundation year 1&2	0.91% (59)	-	-		-
Registrar	22.05% (1,437)	-	-		-
ST1-3	66.32% (4,323)				

The mean (median) age of children included was 3.28 (2.17) years, with 53.5% male and 46.5% female. At presentation, 47.52% of children were triaged as green 'low risk' cases using the MTS (Zachariasse, et al. 2017), 8.88% as yellow, 0.17% as yellow/red, 17.06% as orange, 23.03% as orange/red and 0.39% as red (high risk). MTS classifications were not recorded in 2.9% of patients. Most patients (66.32%) were treated by specialty doctors (ST1-3), followed by registrars or ST4-8 (22.05%), consultants (7.99%), APNPs (2.73%), and Foundation year 1 & 2 doctors (0.91%). The mean (median) time was 15.3 (14.7 mins) between booking and triage, 67.9 (52

mins) between triage and clinical consultation, and 68.4 (70.6 mins) between consultation and discharge. Total mean (median) time in the ED was 151.6 mins (81.3 mins). Approximately 6.46% of patients were admitted as inpatients, 1.42% of which for a single day, 29.78% (two days), 21.51% (three days), and 47.28% (> four days).

Determinants of patient-level costs

Table 9 provides details of patient-level costing. Those aged 0-3 months exhibited a mean treatment cost of £1000.28, [95% CI £82.89-£2,993.37], over 6-fold higher than the least costly group, aged 3-6 years, (£158.97, [95% CI £20.43-£1,596.43]). Use of blood cultures, urine samples, inpatient admission rates, and inpatient length of stay were all statistically significantly increased for those aged 0-3 months, versus all other age groups, as shown in Table 10, and Figures 6 and 7.

Table 9: Health service costs of paediatric febrile illness by sub-group

	Number	Mean	Std. dev	95% CI	Median	IQR	P-value *
Age							
0-3months	129	£1,000.28	£1,469.98	£82.39-£2,993.37	£76.65	£1,834.10	p=0.0001
3-6 months	281	£522.33	£1,737.66	£122.08-£2,123.51	£53.63	£55.70	
6-12 months	1,041	£205.28	£585.18	£28.26-£734.39	£51.29	£21.50	
1-3 years	2,498	£190.44	£594.95	£13.22-£643.89	£51.64	£21.60	
3-6 years	1,547	£158.97	£501.82	£20.43-£1,596.43	£51.29	£19.80	
6-10 years	707	£165.92	£485.04	£11.14-£843.02	£52.98	£20.70	
10-16 years	315	£408.32	£1,030.12	£44.97-£2,188.27	£55.55	£40.90	
Gender							
Male	3,482	£210.17	£600.23	£38.45-£818.68	£51.29	£21.50	

							p=0.0001
Female	3,036	£238.90	£835.77	£14.13-£924.63	£53.16	£23.10	
NICE NG51 heart rate red flag							
Yes	2,797	£259.40	£848.10	£21.76-£1,015.89	£54.03	£24.60	p=0.0001
No	3,721	£196.59	£604.38	£18.36-£699.74	£50.87	£20.30	
NICE NG51 respiratory rate red flag							
Yes	394	£493.92	£1,035.52	£89.16-£2,011.32	£66.67	£70.45	p=0.0001
No	6,124	£206.15	£691.06	£23.71-£737.44	£51.29	£21.50	
Clinical grade							
APNP	178	£109.52	£312.67	£12.74-£741,65	£48.01	£21.80	
Consultant	521	£315.13	£1,344.91	£25.76-£1,536.36	£73.23	£40.70	
FY 1&2	59	£731.78	£913.38	£97.91-£1,125.77	£327.98	£49.90	p=0.0001
Registrar	1,437	£255.40	£702.86	£19.40-£1,045.91	£54.49	£23.80	
ST1-3	4,323	£199.68	£615.00	£12.51-£721.02	£49.77	£28.05	
Afterhours							
Yes	5,798	£222.22	£726.36	£14.77-£776.64	£51.92	£22.40	p=0.0018
No	720	£234.19	£664.61	£11.96-£913.33	£51.65	£22.00	
MTS classification							
Green	3,098	£121.78	£390.33	£15.81-£	£49.43	£19.05	
Yellow	579	£424.43	£1,027.90	£340.69-£508.17	£63.10	£557.35	
Yellow/Red	10	£85.71	£95.24	£71.73-£99.42	£52.33	£16.50	
Orange	1,112	£487.16	£1,209.15	£416.08-£558.24	£68.86	£77.05	p=0.0001
Orange/Red	1,502	£152.13	£491.60	£123.44-£170.56	£51.84	£17.20	
Red	26	£549.42	£813.99	£236.47-£862.35	£76.88	£1,165.85	
Not recorded	191	£292.01	£966.43	£154.93-£429.09	£50.87	£20.40	
Final diagnosis							
Bacterial Infection/syndrome	460	£988.19	£1,781.97	£86.89-£2,971.08	£77.95	£1,757.35	
Viral Infection/syndrome	1,595	£294.52	£797.43	£18.92-£1,082.33	£51.64	£24.25	

p=0.0001

Inflammatory infection/syndrome	74	£582.58	£1,302.26	£37.60-£1,516.05	£63.44	£1,140.65
Other or trivial infection	130	£390.06	£786.27	£22.34-£1,243.30	£64.04	£187.15
Unknown cause	4,259	£103.06	£286.52	£12.40-633.87	£51.29	£18.60
**Kruskal-Wallis test*						

Table 10: Health service utilisation by patient age and MTS score

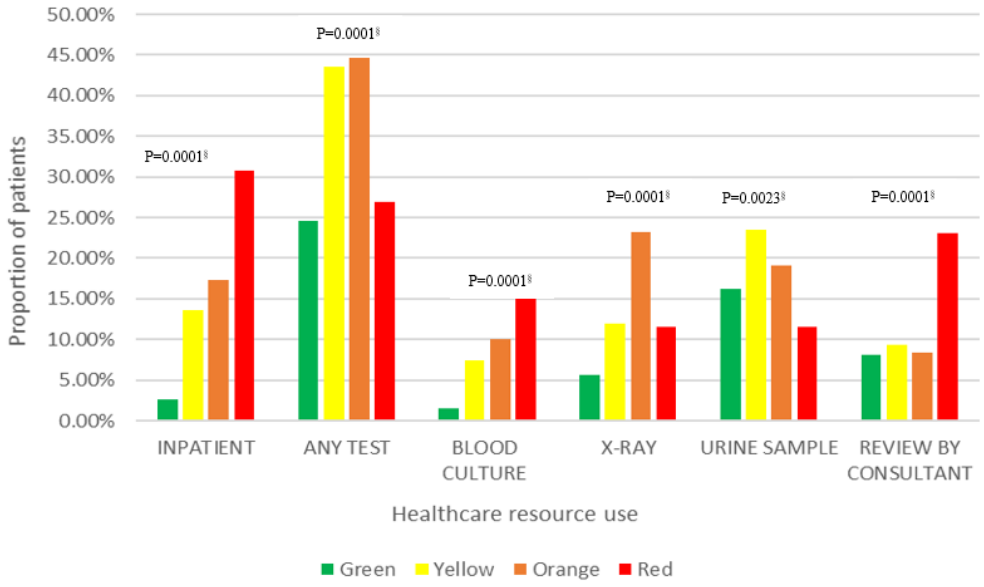
	INPATIENT	LENGTH OF STAY (DAYS)#	ANY TEST	BLOOD CULTURE	X-RAY	URINE SAMPLE	REVIEW BY CONSULTANT
AGE							
0-3 months	34.11%	5.67	51.16%	28.70%	9.30%	39.53%	10.07%
3-6 months	15.66%	5.34	40.92%	11.03%	12.10%	32.74%	5.69%
6-12 months	6.34%	3.83	31.98%	2.01%	9.12%	23.24%	8.64%
1-3 years	5.36%	4.05	29.74%	2.52%	10.88%	18.37%	7.64%
3-6 years	4.01%	4.02	28.70%	3.03%	9.43%	13.70%	8.14%
6-10 years	4.53%	3.78	34.08%	3.67%	9.61%	17.25%	8.76%
10-16 years	7.96%	4.73	42.22%	8.88%	10.15%	15.87%	7.3%
P-value	0.0001§	0.0001*	0.0001§	0.0001§	0.5370§	0.0001§	0.1342§
MTS CLASSIFICATION							
Green	2.61%	3.88	24.59%	1.51%	5.68%	16.17%	8.06%
Yellow	13.64%	4.64	43.52%	7.42%	11.91%	23.48%	9.32%
Orange	17.27%	4.23	44.6%	10.07%	23.2%	19.15%	8.45%
Red	30.77%	2.63	26.92%	15.38%	11.53%	11.53%	23.07%
P-value	0.0001§	0.0001#	0.0001§	0.0001§	0.0001§	0.0023§	

 # Mean length of stay among those admitted for at least one day
**Kruskal-Wallis test*
§ Chi-squared test

Figure 6: Healthcare resource use by age group

§ Chi-squared test

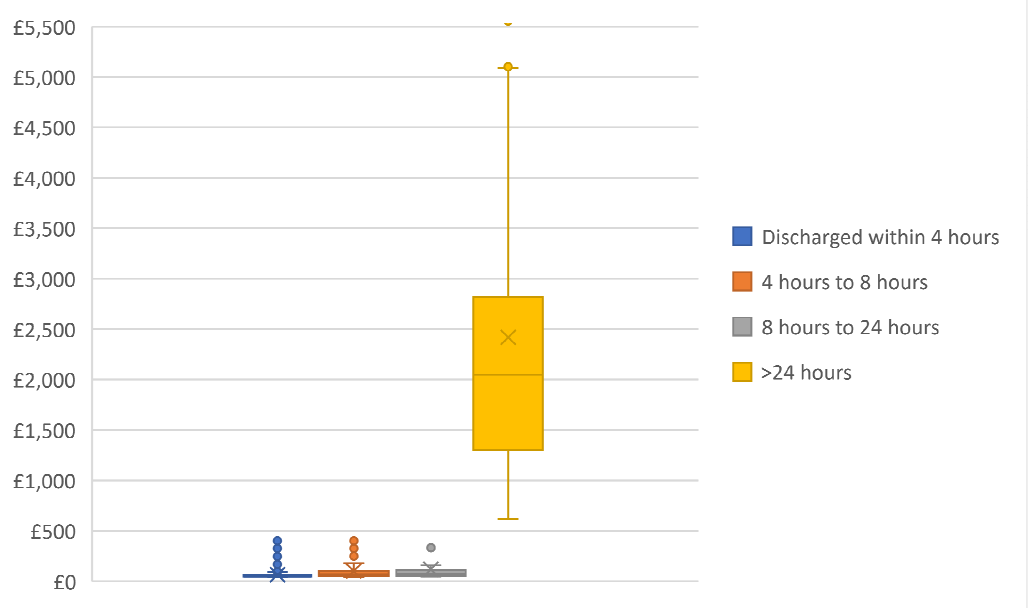
Figure 7: Healthcare resource use by MTS classification



§ Chi-squared test

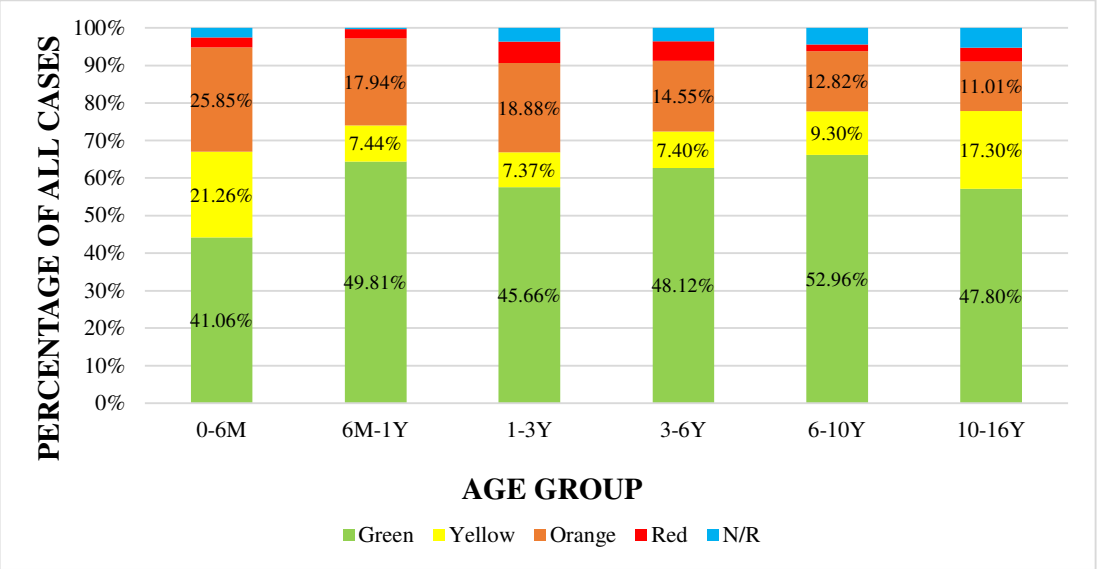
Figure 8 demonstrates how being admitted as an inpatient impacted healthcare costs. Those discharged within the Department of Health's four-hour target exhibited mean (median) healthcare costs of £67 (£51), for those with a four-hour to eight-hour ED stay this increased slightly to £101 (£68), and increasing again to £118 (£72), for those remaining in the ED for between eight-hours and 24-hours. Finally, for those admitted as inpatients and staying more than one-day, mean healthcare costs increased to £2,419 (£2,050).

Figure 8: Healthcare resource use by time in the department



The distribution of MTS classifications was approximately equal across all age-groups, except for those aged 0-6months as shown in Figure 9, 47.11% of which were triaged as yellow or higher.

Figure 9: Distribution of MTS scores by age-group



As expected, overall healthcare expenditure increased with increasing MTS severity, from £121.78 per patient (green), £424.43 (yellow), £487.16 (orange), and £549.42 (red); the majority of which as a direct result of increasing rates of inpatient admission. A one-step increase in triage category, from green to yellow, resulted in a 422% increase in inpatient admission, a 19.6% increase in length of stay for those admitted, and a 391% increase in use of blood cultures. In terms of final diagnoses, bacterial infections were most commonly observed in those aged 0-3 months (15.5%), 3-6months (11.03%) and 10-16 years (11.74%), however the only significant difference was when comparing these groups to those aged 1-3 years (4.6%), $p<0.05$. Those with bacterial aetiologies of fever exhibited over 3-fold higher management costs than those with viral aetiologies (£988.19 vs. £294.52).

Antibiotic prescribing patterns

Approximately 32.4% of febrile children were prescribed antibiotics, of whom 7.05% were retrospectively diagnosed with bacterial aetiologies of fever (Table 11). Approximately 14.9% of patients retrospectively classified as having inflammatory, 10.8% as trivial, and 6.6% as viral aetiologies of fever (probable, definite and viral syndromes), were prescribed potentially avoidable antibiotics, if a means of distinguishing these from bacterial causes of infection been available. Analysing children with viral causes of fever who were triaged as MTS green or yellow (those not deemed to require very urgent or immediate care); those receiving antibiotics spent an additional 53.9 hours as inpatients (57.1 vs. 3.2hours) compared to children with viral aetiologies of fever, triaged MTS green or yellow, who were not prescribed antibiotics. This resulted in a 9.9-fold increase in management costs for those who received potentially avoidable antibiotics (£1,392.30 vs. £140.10) as shown in Table 12; the majority of which attributable to the costs of inpatient or short stay beds for observation.

Table 11: Antibiotic prescribing rates differentiated by age and final diagnosis

	RECEIVING ANTIBIOTICS								
	TOTAL	**0-3 MONTHS**	**3-6 MONTHS**	**6-12 MONTHS**	**1-3 YEARS**	**3-6 YEARS**	**6-10 YEARS**	**10-16 YEARS**	**P-VALUE#**
All	32.4%	27.9%	24.2%	24%	31.9%	37%	34.5%	40.3%	0.0001
Bacterial	89.6%	85%	96.8%	84.3%	93%	89%	87.7%	91.9%	0.3610
Viral	6.6%	20.8%	10%	3.2%	9.4%	4%	2.60%	5.7%	0.0001
Inflammatory	14.9%	0%	0%	0%	9.5%	17.2%	23.1%	12.5%	0.9330
Trivial	10.8%	0%	50%	0%	9.7%	8.1%	20%	5.3%	0.0820
Unknown	36.4%	17.3%	19.2%	25.5%	35.7%	43.3%	42.2%	48.1%	0.0001

Chi-squared test

Table 12: Treatment costs by age, final diagnosis and antibiotic status

	VIRAL		TRIVIAL		INFLAMMATORY		BACTERIAL	
ANTIBIOTICS GIVEN?	*YES*	*NO*	*YES*	*NO*	*YES*	*NO*	*YES*	*NO*
All*	£1,392.30	£140.10	£324.49	£224.54	£185.08	£669.86	£755.03	£747.43
0-3 months	£2,842.60	£479.65	N/A	£113.81	N/A	£50.87	£2,476.96	£2,419.07
3-6 months	£1,969.38	£142.81	£50.39	£334.50	N/A	£65.92	£1,078.39	£60.78
6-12 months	£2,452.83	£159.57	N/A	£58.63	N/A	N/A	£376.20	£774.53
1-3 years	£687.02	£151.09	£2,223.43	£256.88	£51.43	£390.81	£883.52	£278.09
3-6 years	£1,201.76	£123.97	£58.69	£196.88	£54.52	£355.06	£450.45	£586.77
6-10 years	£1,575.80	£63.65	£51.46	£87.65	£475.93	£447.47	£416.84	£672.95
10-16 years	£2,603.54	£143.37	N/A	£401.88	£101.95	£4,842.32	£1,484.10	£694.91

**MTS green and yellow only*

Determinants of increased healthcare expenditure during paediatric febrile episodes

Based on GLM regression, when compared to the reference group of those aged 1-3years, those aged 0-3 months, experienced a 3.54-fold [95% CI 2.59 - 4.85-fold, p<0.0001] increase in healthcare resource use. The presence of a NICE NG51 respiratory rate red flag (NICE 2017) increased costs by 72.1% (p<0.0001). Other factors associated with increased resource use included treatment by FY1/FY2 doctors, which were increased 3.19-fold, relative to the consultant reference group, p<0.0001. When considering only non-urgent children, triaged as green using the MTS, FY1/FY2 doctors exhibited a 7.98-fold increase in costs of management relative to consultants (p<0.0001). FY1/FY2 doctors recorded the highest rates of inpatient admission, ancillary investigations, and referring children to other specialties. Comparing resource use for FY1/FY2 doctors working out-of-hours and those working during regular hours, where the availability of healthcare personnel to perform ancillary investigations may be reduced, there was no significant difference (p=0.9626). Factors including male gender and being treated by an APNP were shown to reduce costs by 15.1% (p=0.0241), and 42.7% (p=0.0112) respectively, as shown in Table 13.

Table 13: Determinants of healthcare resource use for paediatric febrile episodes

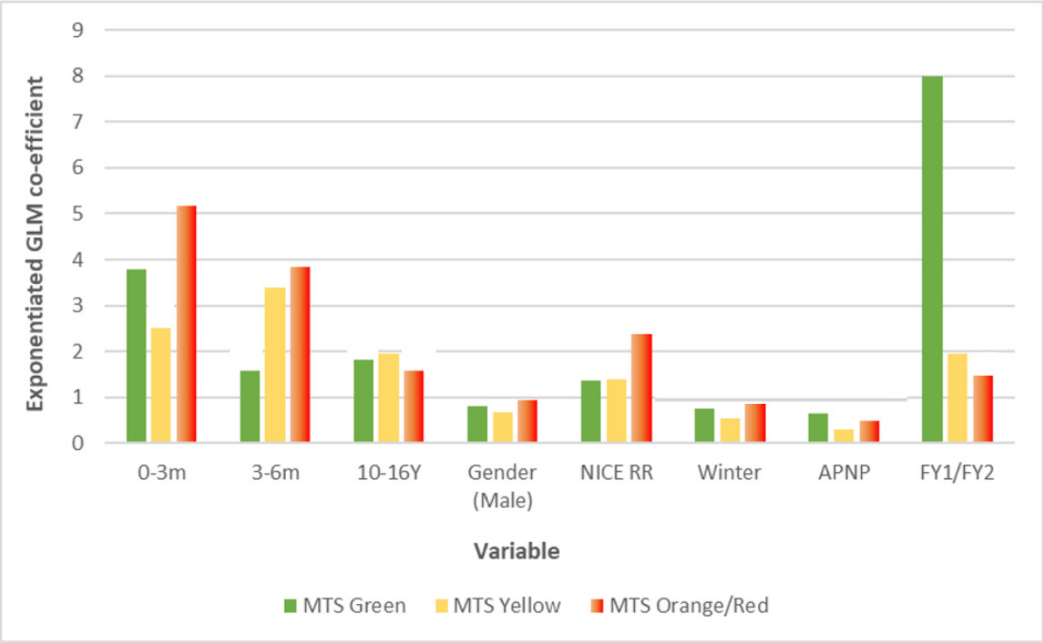
CO-EFFICIENT	LN(β)	EXP (β)	95% CI (β) LOW	95% CI (β) HIGH	P-VALUE
0-3m	1.265	3.543	2.589	4.85	0.001
3-6m	0.791	2.207	1.544	3.155	0.001
6-12m	0.171	1.186	0.924	1.524	0.180
3-6Y	-0.164	0.848	0.705	1.021	0.082
6-10Y	-0.046	0.954	0.738	1.235	0.724
10-16Y	0.656	1.927	1.399	2.654	0.001
Gender (Male)	-0.163	0.849	0.736	0.978	0.024
Time from Book-in to Triage	-0.005	0.994	0.990	0.999	0.013
NICE HR	0.034	1.034	0.894	1.197	0.644
NICE RR	0.543	1.721	1.289	2.299	0.001
Time from Triage to Call in	-0.001	0.999	0.997	1.000	0.357
APNP	-0.555	0.573	0.374	0.878	0.011
FY1/FY2	1.161	3.193	2.017	5.055	0.001
ST1-3	-0.161	0.851	0.670	1.081	0.187
Registrar	-0.068	0.933	0.719	1.212	0.608
After Hours**	0.147	1.159	0.867	1.548	0.317
Winter	-0.215	0.806	0.695	0.934	0.004
MTS Yellow	0.868	2.382	1.905	2.979	0.001
MTS Orange	1.049	2.857	2.397	3.405	0.001
MTS Red	1.096	2.992	1.762	5.081	0.001

*# Figures are exponentiated GLM (gamma, log) coefficients, interpreted as x-fold increases versus the reference group. * Reference group age =1-3 years, reference group clinical grade = consultants, reference group MTS classification = green **Between the hours of 6.30pm and 8a.m Monday to Friday, and all-day Saturday, Sunday and bank holidays.*

Increasing clinical severity, as proxied by increasing MTS classifications, resulted in significant cost increases of 138.2% (2.38-fold), 185.7% (2.85 fold) and 199.2% (2.99-fold) respectively when compared to children triaged as green, (all $p<0.01$). As such, we performed independent GLM regressions for three MTS classifications (green, yellow and orange/red), to account for the possibility that severity of illness may have an important role in determining overall resource use. Similar to the results when

pooling children of all severities, those demonstrated in Figure 10 highlight the consistent importance of ages (<6 months, 10-16 years), prompting a NICE respiratory rate red flag, and being treated by an FY1 or FY2 doctor, suggesting that these are key drivers of increased resource use when managing paediatric febrile illness after taking clinical severity, as proxied by MTS classifications into account.

Figure 10: Determinants of healthcare resource use among febrile children of differing clinical risk/urgency



Sensitivity analysis

The findings were insensitive to changes in the values of the input parameters. Following Monte Carlo simulation and re-running the GLM regression using 100 bootstrapped datasets, the coefficients listed in Table 14 were obtained. Children triaged as MTS Yellow or above, those prompting a NICE NG51 respiratory rate red flag, those treated by an FY1/FY2 doctor, and children aged 0-3 months, 3-6 months

or 10-16 years respectively, were statistically significant predictors of increased healthcare costs in 100% of simulations. Conversely, the cost savings associated with male gender and treatment by an APNP, remained significant in just 8% and 28.3% of simulations respectively.

Table 14: Sensitivity analyses of determinants of healthcare costs for paediatric febrile episodes

	β (BASE-CASE) #	**β (BOOTSTRAPPED MEAN)**	**MINIMUM β (% LOWER) ##**	**MAXIMUM β (% HIGHER) ##**	**STATISTICALLY SIGNIFICANT***
0-3 months	3.543	3.11	2.16 (39.02%)	3.92 (10.69%)	100%
0-6 months	2.207	2.08	1.45 (34.39%)	2.68 (21.55%)	100%
6-12 months	1.186	1.27	1.00 (15.75%)	1.54 (29.84%)	38.38%
3-6 years	0.848	0.88	0.68 (19.3%)	0.98 (15.77%)	19.19%
6-10 years	0.954	1.00	0.74 (22.39%)	1.18 (23.63%)	0%
10-16 years	1.927	1.81	1.25 (35.27%)	2.10 (8.98%)	100%
Gender (Male)	0.849	0.90	0.78 (7.91%)	0.99 (16.64%)	8.08%
Time (Book-in to Triage)	0.994	1.00	0.99 (0.24%)	1.00 (0.65%)	16.16%
NICE HR	1.034	1.03	0.89 (14.04%)	1.12 (8.75%)	0%
NICE RR	1.721	1.65	1.19 (30.71%)	1.99 (15.60%)	100%
Time (Triage to Call in)	0.999	1.00	1.00 (0.14%)	1.00 (0.13%)	3.03%
APNP	0.573	0.69	0.37 (36.23%)	0.99 (72.91%)	28.28%
FY1/FY2	3.193	3.29	1.98 (37.94%)	4.06 (27.11%)	100%
ST1-3	0.851	0.90	0.72 (15.88%)	1.01 (18.17%)	0%
REG	0.933	1.00	0.76 (19.02%)	1.12 (20.10%)	0%
After Hours	1.159	1.19	0.90 (21.98%)	1.47 (26.54%)	2.02%

Winter	0.806	0.79	0.68 (15.08%)	0.89 (10.11%)	98.99%
MTS Yellow	2.382	2.27	1.77 (25.67%)	2.61 (9.59%)	100%
MTS Orange	2.857	2.89	2.23 (22.08%)	3.21 (12.43%)	100%
MTS Red	2.992	4.52	1.95 (34.80%)	6.87 (129.76%)	100%
Constant	164.8	143.50	90.33 (45.19%)	179.37 (8.84%)	100%

 # Figures are exponentiated GLM (gamma, log) coefficients, interpreted as x-fold increases versus the reference group. Reference group age =1-3 years, reference group clinical grade = consultants, reference group MTS classification = green
**Proportion of 100 bootstrapped GLM regressions in which p-value was <0.05*
Higher or lower than base-case estimate

Discussion

Principal findings

This study reports the largest comprehensive prospective observational study to date, assessing the economic implications of diagnostic uncertainty when managing paediatric febrile illness, in those aged 0-16 years in an ED-setting. In a full cohort analysis on the management of this highly common condition, the findings of this chapter have demonstrated that the healthcare resources required to manage this highly common condition are both significant and subject to extensive variation; some of which can be explained by the presence of certain patient and healthcare provider characteristics. Infants aged 0-6 months (particularly those aged 0-3 months), those triaged as MTS yellow or above, and those managed by lesser experienced clinicians (FY1 and FY2), required significantly greater resources in the ED. This was primarily a result of increases in observation time and inpatient length of stay, the latter particularly prominent in those receiving antibiotics. In cases of MTS green and yellow, viral infections, where antibiotics were potentially avoidable if more sensitive and prompt diagnostics had been available at this time, costs increased 9.9-fold (95%

CI 6.48 - 13.2-fold). This was equivalent to an additional £1,352.20 spend per child (all children pooled), rising to £2,363 for infants aged less than three months.

Strengths & limitations of the chapter

This chapter has several strengths. We included more than 6,500 febrile children over all seasons during a one-year period, and by applying TDABC methodology we could achieve significant detail. This resulted in an inclusive and representative estimation of the economic impact of paediatric febrile illness to NHS EDs. Capturing model input data using a prospective time-in-motion approach provided confidence regarding the time requirements of essential components of care in the patient pathway. Data regarding these patient touchpoints are lacking in the literature and we believe this analysis has filled a gap which may subsequently be used for similar health-economic analyses in the future.

Limitations of this chapter include the fact that presumed viral and bacterial aetiologies of fever were applied retrospectively. We therefore lacked the benefit of clinical acumen and the impact of parental anxiety, which could heavily influence the decision to prescribe antibiotics in real-world settings. While we made every effort to minimize bias when coding final diagnoses using the algorithm provided by Herberg et al (Herberg, et al. 2016), there is a possibility that errors could have occurred, which may have affected conclusions regarding potentially avoidable antibiotics in the event of an incorrect diagnosis. However, following random sampling and checking of diagnoses we believe the likelihood of this to be minimal given the level of detail provided and the simplicity in using the diagnosis algorithm. Another potential

limitation is the completeness of the dataset, with just under 24% of observations removed due to missing or incomplete data. While it was assumed that these data were missing at random, we cannot be sure of this, and as such we are unsure how the results may have differed if data for these 2,034 children were available. While we made every effort to ensure a thorough approach to capturing NHS resource use, there were also instances where it was likely that we underestimated costs. Our time-in-motion data did not capture information regarding additional consultations and advice from senior members of staff, which are likely to increase the costs of lesser experienced clinicians managing febrile children; nor did it include the societal costs of febrile illness borne by parents including time off work, especially in the case of hospitalisation.

Considering that new diagnostics may result in a reduction in antibiotic use, it is plausible that reattendances or the amount of time required for observing patients in the department could increase, thereby potentially reducing the value to parents of improved diagnostics. Another limitation is that the cost data used to estimate the economic impact of managing paediatric febrile illness were likely over-estimated. We used net-ingredient costs provided by the NHS, these costs represent baseline costs prior to the negotiation of discounts by Trusts. While this data detailing the precise costs of the consumables and diagnostics used were not publicly available, this remains a limitation as any discounts achieved effectively lower the price of managing the condition. Additionally, while this study reports on the age of the child as a predictor of healthcare costs, it is worth stating that much of the resource use observed, including the use of ancillary investigations, particularly among those aged <3months,

is likely to be a result of the guidelines which suggest this approach (NICE 2017). Therefore, it may not be the age of the child specifically which is a driving factor in determining healthcare costs, but rather the presence of guidelines suggesting more intensive treatment and monitoring for these children. The final limitation of this chapter concerns the generalizability of the findings to other settings, whether in the UK, Europe or further afield. Our data were collected from a single site, and our analysis based on local prescribing protocols. As such, the economic value of improving the management of febrile illness in other settings, including the United States, where are a more consultant-led approach may be more common, may differ from those demonstrated here.

Interpretation considering other evidence

Two previous studies have reported healthcare costs for managing children with SBIs, namely UTI (Hoberman, et al. 1999) and meningococcal disease (Bell, et al. 2015). Similarly, two studies reporting costs of management for children with fever of any cause (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (D. Schriger, L. Baraff, et al. 2000) have been performed in the USA, with data collected at least 5 years ago, in children aged <3 years and <90 days respectively, thereby limiting their generalisability. However, no study prior to the one demonstrated in this chapter has assessed the resource implications of managing fever in a broad and representative cohort of all ages, diagnoses, and types of resource use in Europe.

The finding that infants (particularly those aged <3months) tended to require significantly greater ED resources, may be explained by increased cautiousness and a

lack of symptomatic information provided directly from children themselves. Despite most causes of fever in children being self-limiting, the fear of missing life-threatening infection in children with fever remains a persistent problem for clinicians, who have a natural tendency to be risk-averse (Alpern and Henretig 2006). Commonly reported concerns among clinicians treating febrile children include suspected central nervous system damage (24%), seizures (19%), and death (5%) (Crocetti, Moghbeli and Serwint 2001), manifesting in overly aggressive, and often, in hindsight, clinically unnecessary treatment (Elkon-Tamir, et al. 2017). Additionally, the prevalence of invasive bacterial infections, bacteraemia and bacterial meningitis, are highest in the first 3 months of life, driving clinician behaviour towards a cautious approach among this high-risk group. Clinical prediction rules, such as the Yale observation scale may be useful in these groups, particularly among those with less experience in ruling in/out serious bacterial infections. However, reliability in higher (Nigrovic, Mahajan and Blumberg 2017) vs. lower income countries (Bang and Chaturvedi 2009) is variable, suggesting that these alone may not be enough to fill the diagnostic gap faced by the clinician managing paediatric febrile illness in ED settings (Thompson, Van den Bruel and Verbakel 2012).

Though potentially avoidable antibiotic prescribing was lower in our cohort (6.6% viral, 10.8% trivial illness) than in similar studies based in the United States (36%) (Wilkes, et al. 2009), and Oxford, England (34%) (Harnden, et al. 2007), we found that antibiotic prescribing for those with viral causes of fever was highest in those aged 0-3 (20.8%), and 3-6 months (10%) supporting the suggestion of an increased tendency to be cautious when treating young febrile infants. This resulted not only in

a substantial increase in ED resource use, but also likely increased inconvenience and distress to the children and parents involved, due to potentially unnecessary investigations and treatment. Furthermore, excess use of antibiotics is known to contribute to increasing rates of antimicrobial resistance (AMR) (Bryce, et al. 2016), an important consideration when exploring both the clinical and economic impact of antibiotic prescribing, which the analyses contained within this chapter were unable to quantify.

Given the paucity of published evidence, additional research examining the patient-centred and societal implications of current diagnosis and treatment practices when managing the febrile child, would add considerable value for those looking to determine the true value of improved diagnostics, which may be capable of better targeting of scarce ED resources. Given the variable performance and accuracy of the MTS triage system in paediatric populations, the finding that costs increased with MTS severity is noteworthy. Recent large-scale validation studies have highlighted the low reliability of the MTS in both younger (Zachariasse, et al. 2017), and older children presenting to the ED with fever (van Veen, et al. 2008), with an estimated 54% of children over-triaged when using the MTS (Thompson, Van den Bruel and Verbakel 2012). In adult studies, over-triaging by just a single category, from green to yellow, has been shown to increase the use of electrocardiogram (ECG) and laboratory investigations by 261% and 148% respectively (Santos, Freitas and Martins 2014). Similarly, in our study, children triaged as yellow experienced a 422% increase in inpatient stay, a 76.9% increase in ancillary investigations, and a 15.6% increase in review by consultants, versus those triaged as green. As the MTS categories yellow,

orange and red represent urgent, very urgent and immediate attention respectively, these are the groups with the highest probability of SBIs. The findings of this chapter therefore suggest that these are the groups where novel diagnostics should be targeted.

While we found evidence of an increase in healthcare utilisation among less experienced clinicians (FY1/FY2), just 0.9% of clinicians included in our study were FY1 and FY2 doctors. The results observed in this sample were therefore highly susceptible to bias through a lack of inter-clinician variability, and with a larger sample size may regress towards a lower and perhaps more representative mean. Additionally, although GLM analyses highlighted a 44.2% increase in time spent in the ED for those treated by FY1 and FY2 doctors when compared to consultants, this was likely due to the need to seek second opinions from more experienced colleagues, something which we were unable to attach costs to. This may also have been because lower acuity patients wait the longest and are more likely to be seen by lesser experienced doctors, as the sickest are re-directed to senior doctors. Because it is likely that any advances in diagnostics are likely to be heavily used by, and provide the greatest diagnostic utility to lesser experienced doctors, this could reduce times in the ED, but potentially still increase management costs. This is particularly true if the price of novel POC tests is high, as with multiplex PCR, which may cost the same as a day in hospital when first released. The price of such tests can however be expected to decrease over time, resulting in savings over the longer-term.

Chapter 3 summary

The previous chapter of this thesis found that while fever is a common reason for presentation to paediatric EDs, the relationship between diagnostic uncertainty, healthcare utilisation and healthcare costs, is currently unclear. A small number of studies were identified; however, these were characterised by significant heterogeneity, with highly variable data collection periods, settings, costing methodologies and inclusion criteria. The aim of this chapter was therefore to fill this gap in the literature and empirically explore the real-world economic impact of paediatric febrile illness in ED-settings. The peer-reviewed published version of this Chapter is provided in the Appendix below.

Based on a comprehensive and representative sample of febrile children of varying age, presenting complaints, final diagnoses and treating clinicians, this study has demonstrated that the management of paediatric febrile illness in the ED poses a substantial financial burden. Until now, little was known about both the drivers and extent of resource use for managing this highly common condition. The findings of this chapter suggest that the costs associated with managing paediatric febrile illness in the ED are significant, and predominantly a result of diagnostic uncertainty, which most often leads to in increased observation time and inpatient admission. Children aged 0-6 months, those triaged as MTS yellow and above and those managed by newly qualified doctors are the most likely to receive additional resources in the ED. The findings of this chapter also highlighted that after accounting for the severity of illness, precautionary antibiotic prescribing, particularly in younger low acuity children with viral illnesses, is associated with substantial increases in health service utilization.

This is predominantly because of increases in inpatient admissions. As such, any advances in diagnostic capabilities, including molecular diagnostics, protein biomarkers and POC tests, would likely yield the potentially greatest economic and efficiency gains among these groups. What is unclear however, is how both patient and parent/carer experience and satisfaction with care may change as a result. It is important to acknowledge that decisions made during the management of paediatric febrile illness are not done so purely based on economics, efficiency and reducing the impact of diagnostic uncertainty, but also with regard to satisfaction with care. With the development of more sensitive, accurate and faster diagnostics, processes for investigating febrile illness are likely to change. With this, it can be expected that factors which may matter to parents, such as the likelihood of antimicrobial prescriptions, waiting times, and the experience (and perceived knowledge) of treating clinicians may in some way be affected. What is unclear are the expectations of parents and HCPs alike when managing paediatric febrile illness, and precisely how any changes in management pathways for paediatric febrile illness, will impact both groups. The aim of the following chapter is to address this evidence gap, and explore preferences for both current and future paediatric febrile illness care pathways among both HCPs and parents. As a result, it will be possible to establish the likely impact, advantages, and disadvantages of implementing novel diagnostic modalities for the management of paediatric febrile illness in the ED.

Chapter 3 - Appendix

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RESEARCH ARTICLE Open Access

The cost of diagnostic uncertainty: a prospective economic analysis of febrile children attending an NHS emergency department

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Abstract

Background: Paediatric fever is a common cause of emergency department (ED) attendance. A lack of prompt and definitive diagnostics makes it difficult to distinguish viral from potentially life-threatening bacterial causes, necessitating a cautious approach. This may result in extended periods of observation, additional radiography, and the precautionary use of antibiotics (ABs) prior to evidence of bacterial foci. This study examines resource use, service costs, and health outcomes.

Methods: We studied an all-year prospective, comprehensive, and representative cohort of 6518 febrile children (aged < 16 years), attending Alder Hey Children's Hospital, an NHS-affiliated paediatric care provider in the North West of England, over a 1-year period. Performing a time-driven and activity-based micro-costing, we estimated the economic impact of managing paediatric febrile illness, with focus on nurse/clinician time, investigations, radiography, and inpatient stay. Using bootstrapped generalised linear modelling (GLM, gamma, log), we identified the patient and healthcare provider characteristics associated with increased resource use, applying retrospective case-note identification to determine rates of potentially avoidable AB prescribing.

Results: Infants aged less than 3 months incurred significantly higher resource use than any other age group, at £1000.28 [95% CI £82.39–£2993.37] per child, ($p < 0.001$), while lesser experienced doctors exhibited 3.2-fold [95% CI 2.0–5.1-fold] higher resource use than consultants ($p < 0.001$). Approximately 32.4% of febrile children received antibiotics, and 7.1% were diagnosed with bacterial infections. Children with viral illnesses for whom antibiotic prescription was potentially avoidable incurred 9.9-fold [95% CI 6.5–13.2-fold] cost increases compared to those not receiving antibiotics, equal to an additional £1352.10 per child, predominantly resulting from a 53.9-h increase in observation and inpatient stay (57.1 vs. 3.2 h). Bootstrapped GLM suggested that infants aged below 3 months and those prompting a respiratory rate 'red flag', treatment by lesser experienced doctors, and Manchester Triage System (MTS) yellow or higher were statistically significant predictors of higher resource use in 100% of bootstrap simulations.

(Continued on next page)

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(Continued from previous page)
Conclusion: The economic impact of diagnostic uncertainty when managing paediatric febrile illness is significant, and the precautionary use of antibiotics is strongly associated with increased costs. The use of ED resources is highest among infants (aged less than 3 months) and those infants managed by lesser experienced doctors, independent of clinical severity. Diagnostic advances which could increase confidence to withhold antibiotics may yield considerable efficiency gains in these groups, where the perceived risks of failing to identify potentially life-threatening bacterial infections are greatest.

Keywords: Febrile, Fever, Pyrexia, Children, Health economics, Cost of illness, Antibiotics, United Kingdom

Background

Fever is a common cause of presentation to paediatric emergency departments (EDs) [1], accounting for ~ 20% of all visits [2], but despite its frequent occurrence, the aetiology of fever is diverse [3]. Most children with fever will suffer from self-limiting viral illnesses; however, viral, bacterial, and severe bacterial infections (SBIs) may result in almost identical clinical presentations in infants, making diagnosis based on presentation, history, and clinical judgement alone a difficult task.

While a clear focus of bacterial infection may be present with presentations of acute otitis media (AOM) or urinary tract infection (UTI), occult bacteremia can also occur in children who appear otherwise well, and fever without focus is a common presentation, particularly so in those aged < 36 months [4–6]. However, occurring in as few as 1% of febrile children [4, 5], these 'hidden' bacterial infections represent a needle in the haystack, and the challenge for clinicians is to accurately identify children at risk of bacterial infections. While it is possible that they may resolve spontaneously, for those in whom they do not, life-threatening and potentially life-changing complications can develop [4, 7, 8], with adverse outcomes in each survivor of severe meningococcal disease resulting in lifelong treatment costs of ~ £1.3m [9].

As a result, a cautious stepped approach to the management of the febrile child is common, characterised by extended periods of observation, investigations, radiography, and the precautionary use of antibiotics, often prior to definitive evidence of bacterial foci [10]. Unfortunately, such interventions are invasive, can be painful, and are likely to prolong a child's visit to the ED, contributing to extended ED waiting times and driving the use of scarce ED healthcare resources.

The test currently providing the greatest degree of certainty in diagnosing invasive bacterial infections, the blood culture, typically takes 12–48 h to provide results, has a sensitivity of just 30–40% [11], and a significant false positive rate due to contamination with commensal bacteria from the skin and mucosal surfaces [12]. This limits the diagnostic utility of the blood culture to clinicians required to make decisions concerning the management of the febrile child in real time, which in turn increases the importance of sufficient observation time, blood/urine investigations, and clinical judgement.

With the potential over-treatment of febrile children on the one hand and the prospect of failing to identify potentially life-threatening SBIs on the other, a lack of timely and reliable indicators of febrile aetiology, coupled with a natural tendency for risk aversion when treating children, has resulted in a substantial financial burden to healthcare systems worldwide. However, to date, just a handful of studies, predominantly USA based and conducted between 6 and 25 years ago in young children, have examined the economic impact of paediatric febrile illness [13–16].

Using a bottom-up time-driven and activity-based costing model (TDABC), the aims of this research were to (1) estimate the economic impact of managing febrile illness episodes in children of all ages and presenting complaints, in an NHS paediatric ED setting; (2) identify how management practices and costs vary with factors including patient age, and the experience of treating clinicians; and (3) provide insights regarding where any diagnostic advances currently under development, including molecular diagnostics, protein biomarkers, and point-of-care (POC) testing technologies, are likely to yield the greatest clinical and socioeconomic value, by reducing clinical uncertainty increasing confidence to withhold antibiotics.

Methods

Participants and methods

This study applies time-driven activity-based costing (TDABC), a bottom-up approach to healthcare costing, which maps pathways observed during routine clinical practice, identifies all points and durations of interaction therein, and assigns time-dependent costs to each constituent. The costs of non-time-dependent activities, including tariff-based ancillary investigations, are subsequently added to provide a representative activity-weighted cost per completed treatment episode.

A total of 8552 consecutive febrile children, with a temperature above 38 °C at presentation or below 38 °C with an unverified parent-reported history of fever up to 3 days previous, were prospectively identified. All children visited Alder Hey Children's NHS Foundation Trust, a large paediatric specialist care provider in the North West

of England, between 1 September 2012 and 31 August 2013. Children were excluded (1) if data concerning key components of their stay, including the treatments provided, or healthcare personnel seen, were missing or incomplete or (2) if there were pre-existing medical conditions likely to modify ED care pathways from those of the average 'otherwise well' patient, including paediatric oncology patients.

A schematic of the clinical pathway used for this study is provided in Fig. 1. Children were initially seen by a qualified ED nurse who conducted an initial evaluation, using the Manchester Triage System (MTS) [17]. MTS assessments follow a flow chart based on the patient's reason for contacting the ED. The chart begins by identifying possible criteria indicating life-threatening conditions for the patient, and if none of these conditions are present, the nurse continues along the flow chart asking questions until the nurse assigns the patient an appropriate category. The nurse's experience can contribute to the assessment, but on the other hand, the risk of the nurse missing serious conditions is reduced because the flow chart forces the nurse to ask key questions and make vital inquiries. Children were triaged as green 'standard', yellow 'urgent', orange 'very urgent', or red 'immediate attention'. For several children, borderline 'yellow/red' or 'orange/red' categories were applied. This was a result of uncertainty during triage, and such children had their MTS classification amended with increased or reduced urgency following a second opinion with a nurse or clinician. Diagnostic categories, defined as definite bacterial, probable bacterial or bacterial syndrome with low/no inflammatory markers, definite viral, probable viral, or viral syndrome with no/high inflammatory markers, trivial illness, inflammatory illness, and unknown/insufficient information, were applied retrospectively, based on an adapted algorithm from Herberg et al. [18]. In any instance where uncertainty or disagreement occurred regarding the appropriate classification, these cases were marked and decided upon by two consultants specialising in paediatric infectious disease. All cases had notes, including CRP, neutrophils, and sterile site pathogenic bacteria recorded such that diagnosis classifications could be quality checked, to ensure consistency. For this analysis, definite bacterial, probable bacterial and bacterial syndromes with low/no inflammatory markers, were collectively defined as 'bacterial aetiologies', while definite viral, probable viral, and viral syndromes with no/high inflammatory markers were collectively defined as 'viral aetiologies'. Like other studies [19], the prescription of antibiotics for patients with anything other than a bacterial aetiology of fever was, for this study, defined retrospectively as 'potentially avoidable'.

Because time stamps documenting the duration of contact with healthcare personnel for various treatments and investigations are not routinely collected as part of NHS electronic patient records, these were imputed in one of two ways. Firstly, estimates were provided by staff actively involved in the provision of ED care. Secondly, prospective time-in-motion data were collected for a representative cohort of 71 febrile children presenting to Alder Hey Children's NHS Foundation Trust ED between January 6 and February 12, 2017. Four 5th-year medical students collected the data by 'shadowing' patients reporting to the book-in desk with fever as a symptom. Additionally, any patients suspected of fever by clinical teams (such as the nurse performing an initial visual assessment) were additionally identified. The researchers followed patients through the ED, documenting all points of interaction with healthcare professionals using a stopwatch and a pre-designed case report form. Data were collected in four hourly blocks during the day (8 a.m.–4 p.m.), evening (4 p.m.–12 a.m.), and early morning (12 a.m.–4 a.m.), 7 days a week. All children with a suspected fever were observed from the point of visual assessment, and their experience in the ED, timed using a stopwatch and documented in Microsoft® Excel. For any events which were not observed during implementation of the

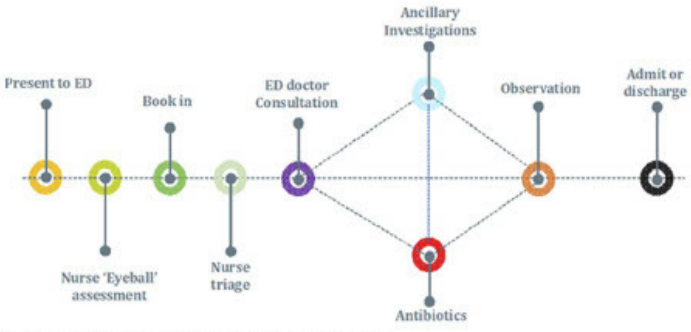

Fig. 1 Clinical pathway of paediatric febrile illness used for patient-level costing

time-in-motion study, including clerical and administrative tasks such as writing up patient notes, these were estimated following a Delphi panel approach. In all such cases, a number of estimates were obtained and the average time was used because tasks, such as inserting a cannula for example, can be expected to take varying lengths of time depending upon factors such as experience, co-operation of the child, state of hydration, or vascular filling. All timings used are provided in Table 1.

Unit costs

Hourly salaries for healthcare personnel were provided by the patient-level costing department at the Trust. Except for clinicians, salaries for those working either (1) at the weekdays between 7 p.m. and 7 a.m. or (2) at the weekend had their hourly rate increased in line with NHS guidance on working unsocial hours [20]. Costs for non-time-driven activities, including laboratory-based investigations, were obtained from the Trust's finance department and NHS reference costs 2015/16 [21].

Pharmaceuticals were assigned unit costs from the British National Formulary. As data concerning the precise antibiotics provided to patients were not available, we assumed that antibiotic prescribing was in line with the recommendations provided within NICE CG160 [22]. Namely, where intravenous (IV) antibiotics were prescribed, both a third-generation cephalosporin (cefotaxime, ceftriaxone) and an anti-listeria agent were provided (amoxicillin, ampicillin) for infants under 1 month, and a third-generation cephalosporin alone if more than 1 month. In cases of empiric IV antibiotic therapy, it was assumed that a third-generation cephalosporin directed against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, and *Haemophilus influenzae* type b was provided. Where oral antibiotics were prescribed, it was assumed that amoxicillin or cephalexin was provided as per local antimicrobial guidance.

Table 1 Staff time associated with components of the paediatric febrile illness pathway

Activity	Mean duration (min)
Triage time (nurse)*	4.5
Clinician consultation time (MTS green)*	16.2
Clinician consultation time (MTS yellow)*	19.4
Clinician consultation time (MTS orange)*	21.1
Clinician consultation time (MTS red)*	22.7
Clinician time—writing up patient notes#	10
Order blood/urine culture (clinician)#	10
Arrange X-ray (clinician)#	6
Book patient into the ED (receptionist)#	2
Refer patient to other specialties (clinician)#	20
Insert cannula (clinician)*	20
Provide antibiotics/other medicines (nurse)#	5
Visual assessment triage (nurse)*	2
Interpret results of ancillary investigations (clinician)#	10

*Collected during time-in-motion study
#Estimate provided by ED consultants

Costs incurred during inpatient stay were obtained from NHS reference costs 2015/16. The tariff HRG PW20C (paediatric fever of unknown origin, CC score = 0) was utilised to reflect a 3-day short stay inpatient admission. As children could be admitted for anywhere between 1 and 72 h under the reference tariff, this figure was divided through by 72 and multiplied by the number of hours of inpatient admission. Patients who exceeded the 3-day limit incurred an excess bed day charge which was applied from the fourth day until discharge [21]. Finally, indirect costs were estimated for each patient, using the 'full absorption approach'. This included the anticipated use of facilities, such as toilets, and the time of administrative staff typing up and sending discharge notes to the patient's general practitioners. Societal costs, including parental absence from work, and children's absence from school were not included, as the analysis was conducted from a healthcare provider perspective. Due to the short time frame of the analysis, costs were not discounted. All unit costs were in 2017 prices and are provided within Table 2.

Outcomes and statistical analysis

We present summary statistics to describe the characteristics of participants. Categorical variables were summarised by frequency and percentage, while continuous variables were reported as mean, standard deviation (SD), median, interquartile range (IQR), and minimum and maximum values. Our primary outcome was the 'cost per completed febrile illness episode', with an 'episode' defined as the period from booking in to the ED to final discharge, enabling the possibility for re-attendances to be included. We additionally performed sub-group analyses to account for patient and healthcare provider heterogeneity. As our primary outcome data were both non-normally distributed, and characterised by sub-groups of unequal size, the Kruskal-Wallis test was applied to assess statistical significance, with Dunn's post hoc pairwise comparison (adjusted by the Holm FWER method) used to determine where significant differences were present. Results were reported as p values and considered statistically significant at the standard 5% level. Multivariate regression analysis using a generalised linear model (GLM) was performed to estimate conditional mean health expenditure and identify covariates associated with increased healthcare utilisation. Because several prior studies have demonstrated that the gamma family with a log error link is not only robust, but also the most commonly applied approach in healthcare cohorts in which positive and skewed healthcare costs are

Table 2 Unit costs by component of paediatric febrile illness pathway

Item	Unit cost
Investigations (per test)	
Amylase	£6.00
Bacterial PCR	£158.00
Bilirubin	£6.00
Biochemistry profile	£8.00
Blood albumin	£6.00
Blood glucose test	£6.00
Blood culture	£35.00
Blood gas[#]	£7.00
Blood taken	£3.00
Calcium profile	£7.00
Clotting screen	£5.00
Creatinine	£6.00
CRP	£6.00
CSF	£6.00
CT scan (head)	£201.00
ECG	£33.00
ENT swab	£19.00
ESR	£4.00
FBC	£3.00
Glandular fever screen	£4.00
Group and save	£12.00
LFTs	£7.00
Magnesium	£6.00
Malarial parasite test	£21.00
Measles PCR	£55.00
Meningo pneumo PCR	£25.00
Meningococci screen	£6.00
Mycoplasma SER	£23.00
Pertussis swab	£9.00
Phosphate	£6.00
Rapid Strep test	£9.00
Renal profile	£46.00
Respiratory PCR	£117.00
RSV screen	£12.00
Ultrasound	£55.00
Urinalysis[#]	£8.00
Urine albumin	£6.00
Urine culture[#]	£8.00
Urine dipstick[#]	£6.00
Urine sample	£8.53
Virus PCR	£56.00
X-ray	£46.00
Antibiotics (per dose/course)	
Amoxicillin 125 mg (suspended)[*]	£1.16
Amoxicillin 125 mg (IV)[*]	£4.34
Amoxicillin 250 mg (susp.)[*]	£1.33
Cefotaxime 195 mg (IM)[*]	£0.48
Cefotaxime 575 mg (IM)[*]	£0.66
Nurse time (per hour)	
Band 5	£15.43
Band 6	£18.95
Band 7	£22.50
Band 8a	£27.39
Doctor time (per hour)	
FY1/FY2	£24.24
ST1-3	£30.79
APNP	£27.39
Registrar	£39.02
Consultant	£76.11
Referral to other specialties	
Surgery	£178.55
Medicine	£272.74
ENT	£146.92
Neuro	£411.78
Inpatient admission	
Short stay (HRG PW20C, 3 days non-elective stay)[#]	£1712
Excess bed day charge[#]	£462

Unit costs provided by Alder Hey Finance Team unless otherwise stated
[#]NHS Reference costs 2016
[*]British National Formulary 2017

guaranteed [23, 24], our analysis also assumed a gamma error distribution with log link.

Finally, because all timings employed within the TDABC were estimates, and therefore subject to one or more of (1) sampling bias, (2) Hawthorne effects, or (3) reporting bias, a distribution of credible times for each patient interaction with healthcare personnel was used in the time-driven and activity-based costing, to reflect the uncertainty inherent to sampling. For all parameters contained within the time-driven and activity-based costing, continuous variables (time in consultation with clinician, days spent as inpatient) were randomly sampled from gamma distributions as explained by Briggs [25]. Dichotomous variables (percentage of triage assessments performed by band 5/6 nurses) were sampled from representative beta distributions constructed from the sample data available, as explained in previous work by Briggs et al. [26]. For estimates reliant on expert

opinion, which were not observed during the time-in-motion study due to a low frequency of occurrence, uniform distributions were sampled in the absence of information concerning the true sample mean and variance. In choosing this distribution, we combined and ranked response data from all healthcare professionals (of varying roles and experience) surveyed, to define lower and upper limits or 'bounding' criterion. Once responses were provided, respondents were informed of responses by other respondents to gauge their belief in the credibility of different responses and ensure that the distributions utilised were plausible. GLM regression modelling was subsequently replicated for 100 bootstrapped costing datasets randomly utilising parameter values from all plausible distributions, for all variables, to assess the sensitivity of the primary outcome, the cost per febrile illness episode, and the resulting GLM coefficients, to changes in the values of underlying input parameters. Details of all distributions utilised are provided in Table 3. All analyses were performed using STATA 14 (StataCorp LP, USA) and Microsoft® Excel™ (Redmond, WA).

Table 3 Distributions used for probabilistic sensitivity analysis

Parameter	Distribution
Time (hours)	
Nurse triage	Gamma (4.69, 0.01)
Proportion performed by band 6 nurses	Beta (16, 55)
Proportion performed by band 5 nurses	1-Beta (16, 55)
Clinical consultation	Gamma (3.9, 0.04)
Clinician writing up patient notes	Uniform (1, 20)
Arrange blood/urine culture	Uniform (1, 25)
Arranging X-ray	Uniform (1, 30)
Receptionist booking patient in	Uniform (1, 5)
Clinician arranging referral	Uniform (1, 25)
Clinician cannulating child	Uniform (5, 35)
Nurse providing antibiotics to child	Uniform (1, 10)
Visual assessment by nurse	Uniform (0.5,5)
Days spent as inpatient (if admitted)	Gamma (3.72, 1.03)
Salary (cost/hour)	
Nurse (band 5)	Uniform (13.36, 17.5)
Nurse (band 6)	Uniform (16.14, 21.77)
Nurse (band 7)	Uniform (19.34, 25.67)
Nurse (band 8a)	Uniform (24.8, 29.99)
Foundation year doctor	Uniform (22.5,26)
ST1-3	Uniform (27, 30.8)
APNP	Uniform (24.8, 29.99)
Registrar	Uniform (36, 41)
Consultant	Uniform (64.8, 87.4)

Results

Descriptive statistics

Eight thousand five hundred fifty-two individual ED attendances were identified over the study period, with 2034 excluded from the analysis due to incomplete data or failing to meet our inclusion criteria. This resulted in a complete dataset of 6518 observations (Table 4). There was no significant difference in observable characteristics between those included and excluded, including but not limited to age, final diagnoses, MTS classification, and temperature.

The mean (median) age of children included was 3.28 (2.17) years, with 53.5% male and 46.5% female. At presentation, 47.52% of children were triaged as green 'low risk' cases using the Manchester Triage System (MTS) [17], 8.88% as yellow, 0.17% as yellow/red, 17.06% as orange, 23.03% as orange/red, and 0.39% as red (high risk). MTS classifications were not recorded in 2.9% of patients. Most patients (66.32%) were treated by specialty doctors (ST1-3), followed by registrars or ST4–8 (22.05%), consultants (7.99%), APNPs (2.73%), and Foundation year 1 and 2 doctors (0.91%). The mean (median) time was 15.3 (14.7 min) between booking and triage, 67.9 (52 min) between triage and clinical consultation, and 68.4 (70.6 min) between consultation and discharge. Total mean (median) time in the ED was 151.6 min (81.3 min). Approximately 6.46% of patients were admitted as inpatients, 1.42% of which for a single day, 29.78% 2 days, 21.51% 3 days, and 47.28% > 4 days.

Determinants of patient-level costs

Table 5 provides details of patient-level resource use and costing. Those aged 0–3 months exhibited a mean treatment cost of £1000.28, [95% CI £82.89–£2993.37], over six-fold higher than the least costly group, aged 3–6 years, (£158.97 [95% CI £20.43–£1596.43]). Use of blood cultures ($p = 0.0312$), urine samples, inpatient admission rates, and inpatient length of stay ($p = 0.0001$) were all statistically significantly increased for those aged 0–3 months, versus all other age groups, as shown in Table 6.

The distribution of MTS classifications was approximately equal across all age groups, except for those aged 0–3 months, 74.41% of which were triaged as yellow or higher. As expected, overall healthcare expenditure increased with increasing MTS severity, from £121.78 per patient (green), £424.43 (yellow), £487.16 (orange), and £549.42 (red), the majority of which as a direct result of increasing rates of inpatient admission. A one-step increase in triage category, from green to yellow, resulted in a 422% increase in inpatient admission, a 19.6% increase in length of stay for those admitted, and a 391% increase in use of blood cultures. In terms of final diagnoses, bacterial infections were most commonly observed in those aged 0–3 months (15.5%), 3–6 months

Table 4 Descriptive statistics of the study participants

	Mean (SD)	Median (IQR)	Min	Max
Age	3.28 (3.09)	2.17 (3.5)	4 days	15.98 years
Gender male (freq)	53.5% (3484)	–	–	–
Temperature	38.7 (1.07)	38.6 (1.7)	35	41.4
Respiratory rate (bpm)	29.95 (9.23)	28 (8)	14	188
Pulse (bpm)	138.7 (25.98)	138 (37)	22	250
Manchester Triage Scale (MTS) classification				
MTS green (freq)	47.52% (3097)	–	–	–
MTS yellow (freq)	8.88% (579)	–	–	–
MTS yellow/red (freq)	0.17% (11)			
MTS orange (freq)	17.06% (1112)	–	–	–
MTS orange/red (freq)	23.03% (1501)			
MTS red (freq)	0.39% (27)	–	–	–
MTS not recorded (freq)	2.9% (191)	–	–	–
Timings				
Time between booking and triage (min)	15.3 (14.7)	11 (18)	0	71
< 10	47.8%			
11–20	24.1%			
21–40	20%			
41–60	5.6%			
> 61	2.5%			
Time between triage and consultation (min)	67.9 (52)	55 (65)	0	609
< 30	26.9%			
31–60	27.7%			
61–120	30.8%			
121–180	11.4%			
181–240	2.6%			
> 240	0.6%			
Time in ED post consultation (min)	68.4 (70.6)	45 (72)	0	630
< 30	43.5%			
30–60	15.1%			
61–120	24.8%			
121–180	9.7%			
> 181	7%			
Total time in ED (min)	151.6 (81.3)	135 (98)	16	729
< 60	8.3%			
61–120	32.7%			
121–240	46.9%			
241–360	9.6%			
> 361	2.5%			
Inpatient length of stay (days)				
Not hospitalised	93.51%			
1–3	3.42%			
4–7	2.43%			
8+	0.63%			

Table 4 Descriptive statistics of the study participants *(Continued)*

	Mean (SD)	Median (IQR)	Min	Max
Re-attendance (freq)	3.43% (224)	–	–	–
Afterhours (freq)	88.9% (5798)	–	–	–
Winter (freq)	60.1% (3918)	–	–	–
Reviewing clinician				
APNP	2.73% (178)	–	–	–
Consultant	7.99% (521)	–	–	–
Foundation years 1 and 2	0.91% (59)	–	–	–
Registrar	22.05% (1437)	–	–	–
ST1-3	66.32% (4323)			

(11.03%), and 10–16 years (11.74%); however, the only significant difference was when comparing these groups to those aged 1–3 years (4.6%), $p < 0.05$. Those with bacterial aetiologies of fever exhibited over threefold higher management costs than those with viral aetiologies (£988.19 vs. £294.52).

Antibiotic prescribing patterns

Approximately 32.4% of febrile children were prescribed antibiotics, of whom 7.05% were retrospectively diagnosed with bacterial aetiologies of fever. Approximately 14.9% of patients were retrospectively classified as having inflammatory, 10.8% as trivial, and 6.6% as viral aetiologies of fever (probable, definite and viral syndromes) were prescribed potentially avoidable antibiotics, if a means of distinguishing these from bacterial causes of infection has been available (Table 7). Analysing children with viral causes of fever who were triaged as MTS green or yellow (those not deemed to require very urgent or immediate care), those receiving antibiotics spent an additional 53.9 h as inpatients (57.1 vs. 3.2 h) compared to children with viral aetiologies of fever, triaged MTS green or yellow, who were not prescribed antibiotics. This resulted in a 9.9-fold increase in management costs for those who received potentially avoidable antibiotics (£1392.30 vs. £140.10) as shown in Table 8, the majority of which attributable to the costs of inpatient or short stay beds for observation.

Determinants of increased healthcare expenditure during paediatric febrile episodes

Based on generalised linear modelling, compared to the reference group of those aged 1–3 years, those aged 0–3 months experienced a 3.54-fold [95% CI 2.59–4.85-fold, $p < 0.0001$] increase in healthcare resource use. The presence of a NICE NG51 respiratory rate red flag [27] increased costs by 72.1% ($p < 0.0001$) (Table 6). Other factors associated with increased resource use included treatment by Foundation year 1/Foundation year 2 (FY1/FY2) doctors, which were increased 3.19-fold, relative to the consultant reference group, $p < 0.0001$. When considering only non-urgent children, triaged as green using the MTS, FY1/FY2 doctors exhibited a 7.98-fold increase in costs of management, relative to consultants ($p < 0.0001$). FY1/FY2 doctors recorded the highest rates of inpatient admission, ancillary investigations, and referring children to other specialties. Comparing resource use for FY1/FY2 doctors working out of hours and those working during regular hours, where the availability of ancillary investigations may be reduced, there was no significant difference ($p = 0.9626$). Factors including male gender and being treated by an APNP were shown to reduce costs by 15.1% ($p = 0.0241$) and 42.7% ($p = 0.0112$) respectively, as shown in Table 9.

Increasing clinical severity, as proxied by increasing MTS classifications, resulted in significant cost increases of 138.2% (2.38-fold), 185.7% (2.85 fold), and 199.2% (2.99-fold) respectively compared to children triaged as green (all $p < 0.01$). As such, we performed independent GLM regressions for three MTS groups (green, yellow, and orange/red), to account for the possibility that severity of illness may have an important role in determining overall resource use. Similar to the results when pooling children of all severities, those demonstrated in Fig. 2 highlight the consistent importance of ages (< 6 months, 10–16 years), prompting a NICE respiratory rate red flag [27], and being treated by an FY1 or FY2 doctor, suggesting that these are key drivers of increased resource use when managing paediatric febrile illness after taking clinical severity into account.

Sensitivity analysis

Our findings were insensitive to changes in the values of our input parameters. Following the Monte Carlo simulation and re-running our generalised linear models on 100 bootstrapped datasets, the coefficients listed in Table 10 were obtained. Children triaged as MTS yellow or above, those prompting a NICE NG51 respiratory rate red flag, and those treated by an FY1/FY2 doctor, and treatment of children

Table 5 Health service costs of paediatric febrile illness by sub-group

	Number	Mean	Std. dev	95% CI	Median	IQR	*p* value*
Age							
0–3 months	129	£1000.28	£1469.98	£82.39–£2993.37	£76.65	£1834.10	
3–6 months	281	£522.33	£1737.66	£122.08–£2123.51	£53.63	£55.70	
6–12 months	1041	£205.28	£585.18	£28.26–£734.39	£51.29	£21.50	
1–3 years	2498	£190.44	£594.95	£13.22–£643.89	£51.64	£21.60	
3–6 years	1547	£158.97	£501.82	£20.43–£1596.43	£51.29	£19.80	$p = 0.0001$
6–10 years	707	£165.92	£485.04	£11.14–£843.02	£52.98	£20.70	
10–16 years	315	£408.32	£1030.12	£44.97–£2188.27	£55.55	£40.90	
Gender							
Male	3482	£210.17	£600.23	£38.45–£818.68	£51.29	£21.50	
Female	3036	£238.90	£835.77	£14.13–£924.63	£53.16	£23.10	$p = 0.0001$
NICE NG51 heart rate red flag [27]							
Yes	2797	£259.40	£848.10	£21.76–£1015.89	£54.03	£24.60	$p = 0.0001$
No	3721	£196.59	£604.38	£18.36–£699.74	£50.87	£20.30	
NICE NG51 respiratory rate red flag [27]							
Yes	394	£493.92	£1035.52	£89.16–£2011.32	£66.67	£70.45	
No	6124	£206.15	£691.06	£23.71–£737.44	£51.29	£21.50	$p = 0.0001$
Clinical grade							
APNP	178	£109.52	£312.67	£12.74–£741.65	£48.01	£21.80	
Consultant	521	£315.13	£1344.91	£25.76–£1536.36	£73.23	£40.70	$p = 0.0001$
FY 1 and 2	59	£731.78	£913.38	£97.91–£1125.77	£327.98	£49.90	
Registrar	1437	£255.40	£702.86	£19.40–£1045.91	£54.49	£23.80	
ST1-3	4323	£199.68	£615.00	£12.51–£721.02	£49.77	£28.05	
Afterhours							
Yes	5798	£222.22	£726.36	£14.77–£776.64	£51.92	£22.40	
No	720	£234.19	£664.61	£11.96–£913.33	£51.65	£22.00	$p = 0.0018$
MTS classification							
Green	3098	£121.78	£390.33	£15.81 - £400.93	£49.43	£19.05	
Yellow	579	£424.43	£1027.90	£340.69–£508.17	£63.10	£557.35	
Yellow/red	10	£85.71	£95.24	£71.73–£99.42	£52.33	£16.50	$p = 0.0001$
Orange	1112	£487.16	£1209.15	£416.08–£558.24	£68.86	£77.05	
Orange/red	1502	£152.13	£491.60	£123.44–£170.56	£51.84	£17.20	
Red	26	£549.42	£813.99	£236.47–£862.35	£76.88	£1165.85	
Not recorded	191	£292.01	£966.43	£154.93–£429.09	£50.87	£20.40	
Final diagnosis							
Bacterial infection/syndrome	460	£988.19	£1781.97	£86.89–£2971.08	£77.95	£1757.35	
Viral infection/syndrome	1595	£294.52	£797.43	£18.92–£1082.33	£51.64	£24.25	
Inflammatory infection/syndrome	74	£582.58	£1302.26	£37.60–£1516.05	£63.44	£1140.65	$p = 0.0001$
Other or trivial infection	130	£390.06	£786.27	£22.34–£1243.30	£64.04	£187.15	
Unknown cause	4259	£103.06	£286.52	£12.40–£633.87	£51.29	£18.60	

*Kruskal-Wallis test

aged 0–3 months, 3–6 months, or 10–16 years respectively, were statistically significant predictors of increased healthcare costs in 100% of simulations. Conversely, the cost savings associated with male gender and treatment by an APNP remained significant in just 8% and 28.3% of simulations respectively.

Table 6 Health service utilisation by patient age and MTS score

	Inpatient	Length of stay (days)[#]	Any test	Blood culture	X-ray	Urine sample	Review by consultant
Age							
0–3 months	34.11%	5.67	51.16%	28.70%	9.30%	39.53%	10.07%
3–6 months	15.66%	5.34	40.92%	11.03%	12.10%	32.74%	5.69%
6–12 months	6.34%	3.83	31.98%	2.01%	9.12%	23.24%	8.64%
1–3 years	5.36%	4.05	29.74%	2.52%	10.88%	18.37%	7.64%
3–6 years	4.01%	4.02	28.70%	3.03%	9.43%	13.70%	8.14%
6–10 years	4.53%	3.78	34.08%	3.67%	9.61%	17.25%	8.76%
10–16 years	7.96%	4.73	42.22%	8.88%	10.15%	15.87%	7.3%
p value	0.0001[$]	0.0001[*]	0.0001[$]	0.0001[$]	0.5370[$]	0.0001[$]	0.1342[$]
MTS classification							
Green	2.61%	3.88	24.59%	1.51%	5.68%	16.17%	8.06%
Yellow	13.64%	4.64	43.52%	7.42%	11.91%	23.48%	9.32%
Orange	17.27%	4.23	44.6%	10.07%	23.2%	19.15%	8.45%
Red	30.77%	2.63	26.92%	15.38%	11.53%	11.53%	23.07%
p value	0.0001[$]	0.0001[#]	0.0001[$]	0.0001[$]	0.0001[$]	0.0023[$]	

[#]Mean length of stay among those admitted for at least 1 day
[*]Kruskal-Wallis test
[$]Chi-squared test

Discussion

This study reports the largest comprehensive, prospective observational study to date, assessing the economic implications of diagnostic uncertainty when managing paediatric febrile illness, in those aged 0–16 years, in an ED setting. In a full cohort analysis on the management of this highly common condition, we demonstrate that the healthcare resources required to manage this condition are both significant and subject to extensive variation, some of which can be explained by the presence of certain patient and healthcare provider characteristics. Infants aged 0–6 months (particularly those aged 0–3 months), those triaged as MTS yellow or above, and those managed by lesser experienced clinicians (FY1 and FY2) required significantly greater resources in the ED. This was primarily a result of increases in observation time for patients and inpatient length of stay, the latter particularly prominent in those receiving antibiotics. In cases of MTS green and yellow viral infections, where antibiotics were potentially avoidable, provided more sensitive and prompt diagnostics had been available at this time, costs increased 9.9-fold (95% CI 6.48–13.2-fold). This was equivalent to an additional £1352.20 spend per patient (all patients pooled), rising to £2363 for infants aged less than 3 months.

Our study had several strengths. We included more than 6500 febrile children over all seasons during a 1-year period, and by applying TDABC methodology, we could achieve significant detail regarding actual resource use. This resulted in an inclusive and representative estimate of the economic impact of paediatric febrile illness to NHS EDs. Capturing model input data using a prospective time-in-motion approach provided confidence regarding the time requirements of essential components of care in the patient pathway. Data regarding these patient touchpoints are not currently available in

Table 7 Antibiotic prescribing rates differentiated by age and final diagnosis

	Receiving antibiotics								
	Total (%)	0–3 months (%)	3–6 months (%)	6–12 months (%)	1–3 years (%)	3–6 years (%)	6–10 years (%)	10–16 years (%)	*p* value[#]
All	32.4	27.9	24.2	24	31.9	37	34.5	40.3	0.0001
Bacterial	89.6	85	96.8	84.3	93	89	87.7	91.9	0.3610
Viral	6.6	20.8	10	3.2	9.4	4	2.60	5.7	0.0001
Inflammatory	14.9	0	0	0	9.5	17.2	23.1	12.5	0.9330
Trivial	10.8	0	50	0	9.7	8.1	20	5.3	0.0820
Unknown	36.4	17.3	19.2	25.5	35.7	43.3	42.2	48.1	0.0001

[#]Chi-squared test

Table 8 Treatment costs differentiated by age, final diagnosis, and antibiotic status

	Viral		Trivial		Inflammatory		Bacterial	
Antibiotics given?	Yes	No	Yes	No	Yes	No	Yes	No
All*	£1392.30	£140.10	£324.49	£224.54	£185.08	£669.86	£755.03	£747.43
0–3 months	£2842.60	£479.65	N/A	£113.81	N/A	£50.87	£2476.96	£2419.07
3–6 months	£1969.38	£142.81	£50.39	£334.50	N/A	£65.92	£1078.39	£60.78
6–12 months	£2452.83	£159.57	N/A	£58.63	N/A	N/A	£376.20	£774.53
1–3 years	£687.02	£151.09	£2223.43	£256.88	£51.43	£390.81	£883.52	£278.09
3–6 years	£1201.76	£123.97	£58.69	£196.88	£54.52	£355.06	£450.45	£586.77
6–10 years	£1575.80	£63.65	£51.46	£87.65	£475.93	£447.47	£416.84	£672.95
10–16 years	£2603.54	£143.37	N/A	£401.88	£101.95	£4842.32	£1484.10	£694.91

*MTS green and yellow only

published literature, and we believe this analysis has filled a gap which may subsequently be used for similar health economic analyses in the future.

Limitations of our study include the fact that presumed viral and bacterial aetiologies of fever were applied retrospectively; therefore, we lacked the benefit of clinical acumen and parental anxiety which could heavily influence the decision to prescribe antibiotics. While we made every effort to minimise bias when coding final diagnoses using the algorithm provided by Herberg et al. [18], there is a possibility that errors could have occurred, which may have affected conclusions regarding potentially avoidable antibiotics in the event of an incorrect diagnosis. However, following random sampling and checking of diagnoses, we believe the likelihood of this to be minimal given the level of detail provided and simplicity in using the diagnosis algorithm. Another potential limitation is the completeness of the dataset, with just under 24% of observations removed due to missing or incomplete data. While it was assumed that these

Table 9 Determinants of healthcare resource use for paediatric febrile episodes

Coefficient	Ln(β)	Exp (β)	95% CI (β) low	95% CI (β) high	*p* value
0–3 months	1.265	3.543	2.589	4.85	0.001
3–6 months	0.791	2.207	1.544	3.155	0.001
6–12 months	0.171	1.186	0.924	1.524	0.180
3–6 years	−0.164	0.848	0.705	1.021	0.082
6–10 years	−0.046	0.954	0.738	1.235	0.724
10–16 years	0.656	1.927	1.399	2.654	0.001
Gender (male)	−0.163	0.849	0.736	0.978	0.024
Time from book-in to triage	−0.005	0.994	0.990	0.999	0.013
NICE HR	0.034	1.034	0.894	1.197	0.644
NICE RR	0.543	1.721	1.289	2.299	0.001
Time from triage to call in	−0.001	0.999	0.997	1.000	0.357
APNP	−0.555	0.573	0.374	0.878	0.011
FY1/FY2	1.161	3.193	2.017	5.055	0.001
ST1-3	−0.161	0.851	0.670	1.081	0.187
Registrar	−0.068	0.933	0.719	1.212	0.608
After hours**	0.147	1.159	0.867	1.548	0.317
Winter	−0.215	0.806	0.695	0.934	0.004
MTS yellow	0.868	2.382	1.905	2.979	0.001
MTS orange	1.049	2.857	2.397	3.405	0.001
MTS red	1.096	2.992	1.762	5.081	0.001

[#]Figures are exponentiated GLM (gamma, log) coefficients, interpreted as *x*-fold increases versus the reference group
*Reference group age = 1–3 years, reference group clinical grade = consultants, reference group MTS classification = green
**Between the hours of 6.30 p.m. and 8 a.m. Monday to Friday, and all-day Saturday, Sunday, and bank holidays

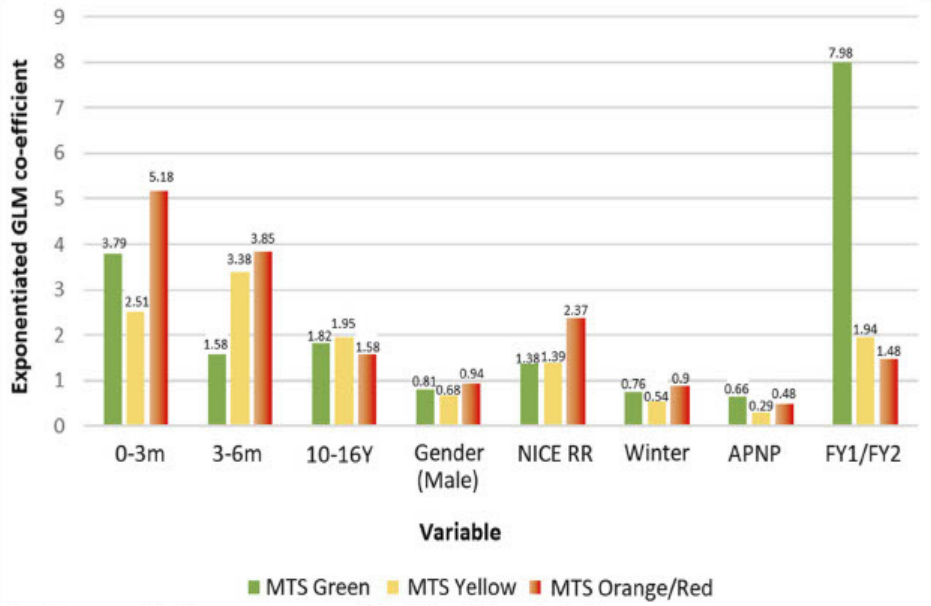

Fig. 2 Determinants of healthcare resource use among febrile children of differing clinical risk/urgency

data were missing at random, we cannot be sure of this, and as such, we are unsure how the results may have differed if data for these 2034 children were available. While we made every effort to ensure a thorough approach to capturing NHS resource use, there were also instances where we likely underestimated costs. Our time-in-motion data did not capture information regarding additional consultations and advice from senior members of staff, which are likely to increase the costs of lesser experienced clinicians managing febrile children, nor did it include the societal costs of febrile illness borne by parents, including time off work, especially in the case of hospitalisation. Considering that new diagnostics may result in a reduction in antibiotic use, it is plausible that re-attendances or time observing patients in the department could increase, thereby potentially reducing the value to parents of improved diagnostics. The final limitation of our study concerns the generalizability of the findings to other settings, whether in the UK, Europe, or further afield. Our data were collected from a single site, and our analysis based on local prescribing protocols, as such, the economic value of improving the management of febrile illness in other settings, including the USA, where are a more consultant-led approach may be more common, may differ from those demonstrated here.

Two previous studies have reported healthcare costs for managing children with SBIs, namely UTI [13] and meningitis [14]. Two studies reporting costs of management for children with fever of any cause [15, 16] have been performed in the USA, with data collected at least 5 years ago, in children aged < 3 years and < 90 days respectively, thereby limiting their generalisability. Additionally, one study conducted in Switzerland demonstrates the cost of illness associated with paediatric community-acquired pneumonia in 2010 [28]. However, no study prior to ours has assessed the resource implications of managing fever in a broad and representative cohort of all ages, diagnoses, and types of resource use in Europe.

The finding that infants (particularly those aged < 3 months) tended to require significantly greater ED resources may be explained by increased cautiousness and a lack of symptomatic information directly from the children themselves, when managing febrile infants. Despite most causes of fever in children being self-limiting, the fear of missing life-threatening infection in children with fever remains a persistent problem for clinicians, who have a natural tendency to be risk averse [29]. Commonly reported concerns among clinicians treating febrile children include suspected central nervous system damage (24%), seizures (19%), and death (5%) [30], manifesting in overly aggressive, and often, in hindsight, unnecessary treatment [31]. Additionally, the prevalence of invasive bacterial infections, bacteraemia and bacterial meningitis, is highest in the first 3 months of life, driving clinician behaviour towards a cautious approach in this high-risk group. Clinical

Table 10 Sensitivity analyses of determinants of healthcare costs for paediatric febrile episodes

	β (base-case)[#]	β (bootstrapped)	Minimum β (% lower)[#]	Maximum β (% higher)[#]	Statistically significant[*] (%)
0–3 months	3.543	3.11	2.16 (39.02%)	3.92 (10.69%)	100
0–6 months	2.207	2.08	1.45 (34.39%)	2.68 (21.55%)	100
6–12 months	1.186	1.27	1.00 (15.75%)	1.54 (29.84%)	38.38
3–6 years	0.848	0.88	0.68 (19.3%)	0.98 (15.77%)	19.19
6–10 years	0.954	1.00	0.74 (22.39%)	1.18 (23.63%)	0
10–16 years	1.927	1.81	1.25 (35.27%)	2.10 (8.98%)	100
Gender (male)	0.849	0.90	0.78 (7.91%)	0.99 (16.64%)	8.08
Time (book-in to triage)	0.994	1.00	0.99 (0.24%)	1.00 (0.65%)	16.16
NICE HR	1.034	1.03	0.89 (14.04%)	1.12 (8.75%)	0
NICE RR	1.721	1.65	1.19 (30.71%)	1.99 (15.60%)	100
Time (triage to call in)	0.999	1.00	1.00 (0.14%)	1.00 (0.13%)	3.03
APNP	0.573	0.69	0.37 (36.23%)	0.99 (72.91%)	28.28
FY1/FY2	3.193	3.29	1.98 (37.94%)	4.06 (27.11%)	100
ST1-3	0.851	0.90	0.72 (15.88%)	1.01 (18.17%)	0
REG	0.933	1.00	0.76 (19.02%)	1.12 (20.10%)	0
After hours	1.159	1.19	0.90 (21.98%)	1.47 (26.54%)	2.02
Winter	0.806	0.79	0.68 (15.08%)	0.89 (10.11%)	98.99
MTS yellow	2.382	2.27	1.77 (25.67%)	2.61 (9.59%)	100
MTS orange	2.857	2.89	2.23 (22.08%)	3.21 (12.43%)	100
MTS red	2.992	4.52	1.95 (34.80%)	6.87 (129.76%)	100
Constant	164.8	143.50	90.33 (45.19%)	179.37 (8.84%)	100

Reference group age = 1–3 years, reference group clinical grade = consultants, reference group MTS classification = green
[#]Figures are exponentiated GLM (gamma, log) coefficients, interpreted as x-fold increases versus the reference group
[*]Proportion of 100 bootstrapped GLM regressions in which *p* value was < 0.05

prediction rules, such as the Yale observation scale may be useful in these groups, particularly among those with less experience in ruling in/out serious bacterial infections; however, reliability in higher [32] vs. lower income countries [33] is variable, suggesting that these alone may not be enough to fill the diagnostic gap faced by the clinician managing paediatric febrile illness [34].

Though potentially avoidable antibiotic prescribing was lower in our cohort (6.6% viral, 10.8% trivial illness) than in similar studies based in the USA (36%) [35] and Oxford, England (34%) [36], we found that antibiotic prescribing for those with viral causes of fever was highest in those aged 0–3 (20.8%), and 3–6 months (10%) supporting our finding of an increased tendency to be cautious when treating young febrile infants. This resulted in not only a substantial increase in ED resource use, but also likely increased inconvenience and distress to the children and parents involved, due to potentially unnecessary investigations and treatment. Furthermore, excess use of antibiotics is known to contribute to increasing rates of antimicrobial resistance (AMR) [37], an important component of both the clinical and economic impact of AB prescribing which we were unable to quantify in this analysis.

Given the paucity of published evidence, additional research examining the patient-centred and societal implications of current diagnosis and treatment practices when managing the febrile child would add considerable value for those looking to determine the true value of improved diagnostics, which may be capable of better targeting of scarce ED resources. Given the variable performance and accuracy of the MTS triage system in paediatric populations, we believe our finding that costs increased with MTS severity is noteworthy. Recent large-scale validation studies have highlighted the low reliability of the MTS in both younger [17] and older children presenting to the ED with fever [38], with an estimated 54% of children over-triaged when using the MTS [34]. In adult studies, over-triaging by just a single category, from green to yellow, has been shown to increase the use of electrocardiogram (ECG) and laboratory investigations by 261% and 148% respectively [39]. Similarly, in our study, children triaged as yellow experienced a 422% increase in inpatient stay, a 76.9% increase in ancillary investigations, and a 15.6% increase in review by consultants, versus those triaged as green. As the MTS categories yellow, orange, and red represent urgent, very urgent, and immediate attention respectively, these are the

groups with the highest probability of SBIs, we believe these are the groups where novel diagnostics should be targeted.

While we found evidence of an increase in healthcare utilisation among the least experienced clinicians (FY1/FY2), just 0.9% of clinicians included in our study were FY1 and FY2 doctors. The results observed in this sample were therefore highly susceptible to bias through a lack of inter-clinician variability, and with a larger sample size may regress towards a lower mean. Additionally, although GLM analyses highlighted a 44.2% increase in time spent in the ED for those treated by FY1 and FY2 doctors when compared to consultants, this was likely due to the need to seek second opinions from more experienced colleagues, something which we were unable to attach costs to. This may also have been because lower acuity patients wait the longest and are more likely to be seen by lesser experienced doctors, as the sickest are re-directed to senior doctors. Because it is likely that any advances in diagnostics are likely to be heavily used by lesser experienced doctors, this could reduce times in the ED, but potentially still increase management costs. This is particularly true if the price of novel POC tests is high, as with multiplex PCR, which may cost the same as a day in the hospital when first released. The price of such tests can however be expected to decrease over time, resulting in savings over the longer term.

Conclusions

In conclusion, based on a comprehensive and representative sample of febrile children of varying age, presenting complaints, final diagnoses, and treating clinicians, this study has shown that the management of paediatric febrile illness in the ED poses a substantial financial burden. This is predominantly due to the impact of diagnostic uncertainty, which most often leads to in increased observation time and inpatient admission. Children aged 0–6 months, those triaged as MTS yellow and above, and those managed by newly qualified doctors are the most likely to receive additional resources in the ED. After accounting for the severity of illness, precautionary antibiotic prescribing, particularly in younger low acuity children with viral illnesses, is associated with substantial increases in health service utilisation, predominantly because of increases in inpatient admissions. So far, information on potential shifts in infection epidemiology, such as an increase in healthcare-associated infections or reductions in vaccine-preventable infections or increases in invasive disease due to serotype replacement, are unlikely to affect our conclusions. Comparable settings in the UK and elsewhere will likely show similar patterns in resource use. Any advances in diagnostic capabilities, including molecular diagnostics, protein biomarkers, and POC tests would likely yield the potentially greatest efficiency gains in these groups of children, as among these the perceived risks of untimely diagnosis are greatest.

Abbreviations

95% CI: 95% confidence interval; AB: Antibiotic; AOM: Acute otitis media; APNP: Advanced paediatric nurse practitioner; CRP: C-reactive protein; ECG: Electrocardiogram; ED: Emergency department; FY1/FY2: Foundation year 1/Foundation year 2; GLM: Generalised linear model; IQR: Interquartile range; MTS: Manchester Triage System; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; POC: Point of care; SBI: Serious bacterial infection; SD: Standard deviation; ST1-3: Specialised training years 1–3; TDABC: Time-driven and activity-based costing; USA: United States of America; UTI: Urinary tract infection

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Availability of data and materials

The data that support the findings of this study are available from the authors upon reasonable request.

Authors' contributions

EDC and LN devised the study and will act as guarantors for the paper. AG supervised the collection of data. EH, NM, LH, JBM, NMOC, YR, SS, SD, and HD helped collect the data. SL, BF, and FC planned and performed all statistical analyses, with SL conducting all costings and data cleaning. JD collected the costing data, and KE collected the additional electronic patient data. SL wrote the first draft of the manuscript and revised and approved the final manuscript as submitted. All authors helped draft the manuscript and approved the final submitted version.

Ethics approval and consent to participate

Ethical approval was the study was granted by North West 9 Research Ethics Committee.
REC reference number: 10/H1014/53. Parental consent was obtained prior to data collection.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Chapter 3 – Publication contribution statement

EDC and LN devised the study and will act as guarantors for the paper. AG supervised the collection of clinical data. EH, NM, LH, JBM, NMOC, YR, SS, SD, and HD helped collect time-in-motion data. SL, BF, and FC planned and SL performed all statistical and economic analyses, with SL conducting all costings, data cleaning and validation. JD collected the original costing data, and KE collected the additional electronic patient data. SL wrote the first draft of the manuscript and revised and approved the final manuscript as submitted. All authors helped draft the manuscript and approved the final submitted version. SL planned and conducted all additional analyses not included in the published manuscript, but included within this chapter of the thesis.

Chapter 4: What matters when managing paediatric febrile illness in the ED? A mixed-methods assessment conducted among parents & healthcare providers

Abstract

Background Fever among children is a leading cause of ED attendance and a diagnostic conundrum, while also contributing significantly towards healthcare expenditure and parental anxiety. Despite the high prevalence and budget impact of managing this highly common condition, robust qualitative and quantitative evidence regarding the preferences of parents and healthcare providers (HCPs) for managing fever in children is scarce. The aim of this chapter is therefore to determine both parental and HCP preferences for the management of paediatric febrile illness in ED-settings.

Methods A multi-phase iterative study design was used where each phase of the research built upon the last. In the first-phase eight focus-groups were conducted in six locations across the Northwest of England (three in Merseyside, two in Lancashire, and one in West Yorkshire), from June-2018 to July-2018. The aim of the focus-groups was to determine what matters to parents when their child is in the ED with a fever. Secondly, coin-ranking exercises were used among parents to prioritise the themes identified during the focus-groups. Next a discrete-choice experiment (DCE)

was conducted with parents, which included the themes identified during the focus-groups, and which were prioritised as most important to parents during the coin-ranking exercise. The DCE survey was conducted with parents in five children's centres in the Northwest of England. Finally, the DCE, which was designed by parents, was also provided to HCPs who were recruited from a paediatric ED in the Northwest of England, to explore any differences in preferences for the management of paediatric febrile illness. The DCE required respondents to choose their preferred option of several hypothetical management scenarios for paediatric febrile illness, with differing levels of; visit time, out-of-pocket costs, antibiotic prescribing, HCP grade and pain/discomfort from investigations.

Results In total, 40 parents took part in the focus-groups. The average focus-group size was 4-5 participants (range 3-7), with a mean duration of 27.4 minutes (range 18-46 minutes). All parents taking part in the focus-groups also completed the ranking-exercise. Following this, 98 parents of children aged 0-11 years, and 99 HCPs took part in the next phase of the research, the DCE. Response rates to the DCE among parents and HCPs were 94.2% and 98.2% respectively. Avoiding pain from diagnostics, receiving a faster diagnosis and minimising wait times were major concerns for both parents and HCPs, with parents willing-to-pay £16.89 for every one-hour reduction in waiting times. Both groups preferred treatment by consultants and nurse practitioners to treatment by doctors in postgraduate training. Parents were willing to trade-off considerable increases in waiting times (24.1mins) to be seen by

consultants and to avoid additional pain from diagnostics (45.6mins). Reducing antibiotic prescribing was important to HCPs but not to parents.

Interpretation Both parents and HCPs care strongly about reducing visit time, avoiding pain from invasive investigations, and receiving diagnostic insights faster when managing paediatric febrile illness in the ED. However, only HCPs were concerned with reducing antibiotic prescribing. Therefore, provided that they are accompanied by initiatives to manage expectations around antibiotics among parents, overdue advances in diagnostic capabilities should improve both child and carer experience and HCP satisfaction considerably when managing paediatric febrile illness in the ED.

Background

In the previous chapter, an empirical examination of the economic implications of diagnostic uncertainty when managing paediatric febrile illness in the ED, was performed for the first time. This was among a highly heterogeneous and representative cohort of febrile children, in a UK-setting. The findings demonstrated a clear link between a lack of diagnostic modalities of sufficient sensitivity and timeliness, subsequent diagnostic uncertainty, and therefore, increases in both resource use and management costs, which may be avoided in the event of improved confidence in diagnostic processes.

It is important to acknowledge that decisions made during the management of paediatric febrile illness are not done so purely based on economics and efficiency, but rather with respect to "what feels right", using clinical acumen, previous experiences and observations to determine the appropriate course of action. Other factors also play a role, including parental anxiety, parental expectations and pressures, and conversely, bed pressures. Therefore, decisions made regarding the management of paediatric febrile illness, not only aim to reduce the impact of diagnostic uncertainty, but also contribute to patient and carer satisfaction with care.

Over the past 10 years there has been increasing interest in ''consumer satisfaction'' in the NHS, starting with the Patients' Charter of 1991 (Stocking 1991), and culminating in the NHS long term plan. The essence of the NHS Plan was to make patients' views and interests the driving force behind reform (NHS 2019).

With the NHS' renewed emphasis on moving towards patient-centric care, and the ability of recipients of healthcare to feedback and co-decide on treatment options, it is important to understand how any diagnostic innovations or changes to the way febrile children are managed in the ED, may therefore be received by children, parents and families. Similarly, it is also important to understand the facets of existing care processes which result in satisfaction or dissatisfaction among recipients and providers of care alike, and how, if at all these may be improved upon. Few clinicians would disagree with the idea that improving patient/carer satisfaction is a desirable end in itself; while other benefits may include a reduced tendency for patients to seek further opinions (Tattersall, et al. 2009) (Mellink, et al. 2003) (Sato, et al. 1999), and a reduced incidence of complaints and litigation (Stelfox, et al. 2005). Additionally, by seeking

the views of relevant health professionals, in this instance healthcare staff working in EDs, related benefits may include improved morale and job satisfaction among these individuals, which itself, is then observed, and experienced positively by patients and carers alike.

Previous research has highlighted several potential themes of importance to both parents and healthcare providers when either receiving or providing care for conditions associated with febrile illness. Examples include parental anxiety (Alkhaldi, Al-Mahmoud and Kanaan 2015) (Brookes-Howell, et al. 2013) (Dwibedi, et al. 2015) and fear of serious, but rare illness, including sepsis (Crocetti, Moghbeli and Serwint 2001). Additionally, the perceived likelihood of infection and even death, can often result in parents of febrile children expecting antibiotics even when not clinically indicated (Rousounidis, Papaevangelou, et al. 2011) (Mustafa, Wood, et al. 2014). Beliefs regarding the assumed efficacy of antimicrobials in treating viral illnesses, including the common cold (McNulty, et al. 2019) (Cabral, et al. 2016) (Chan and Tang 2006) (Abobotain, et al. 2013), in addition to previous experience of their child receiving antibiotics in the past for a similar illness, are some of the many factors driving the demand for antibiotics.

Additionally, some parents may prefer their child to be managed by a more experienced clinician (Chen, Zou and Shuster 2017) (Haron and Ibrahim 2012), or similarly, by a doctor rather than a nurse (Paddison, et al. 2018). Each of these preferences may be fuelled at least in some part, by assumptions regarding the training and competence of healthcare professionals (Paddison, et al. 2018). Others have reported that waiting times (Thompson, et al. 1996) (Thompson, Yarnold and Adams,

et al. 1996), communication (Taylor and Benger 2004), and the avoidance of pain (Nairn, et al. 2004), particularly as a result of procedures such as venous blood sampling (Arıkan and Esenay 2020), may also impact patient and carer experience in the ED.

With the development of more sensitive, accurate and faster diagnostics, processes for investigating febrile illness are likely to change. With this, it can be expected that factors which may matter to parents, such as the likelihood of antimicrobial prescriptions, waiting times, and the experience (and perceived knowledge) of treating clinicians, may in some way be affected. What is unclear however, are the expectations of parents and HCPs alike when managing paediatric febrile illness and precisely how any changes in management pathways for paediatric febrile illness, will impact both groups. Utilising an iterative process of linked studies, where one informs the next, the aim of this chapter is to assess the preferences of both parents and HCPs when managing paediatric febrile illness, and determine both existing and 'potential' satisfaction with care, under a range of plausible scenarios with diagnostics of varying characteristics. The chapter starts with a brief targeted literature review, which informs a series of focus-groups, leading to a ranking exercise and finally a discrete choice experiment (DCE). In doing so, this chapter will examine preferences for existing and future paediatric febrile illness care pathways among both HCPs and parents. As a result, it will be possible to establish the likely impact, advantages, and disadvantages of implementing novel diagnostic modalities for the management of paediatric febrile illness in the ED. The findings of this chapter were published in Archives of Disease in Childhood in August 2020 (Leigh, Robinson, et al. 2020).

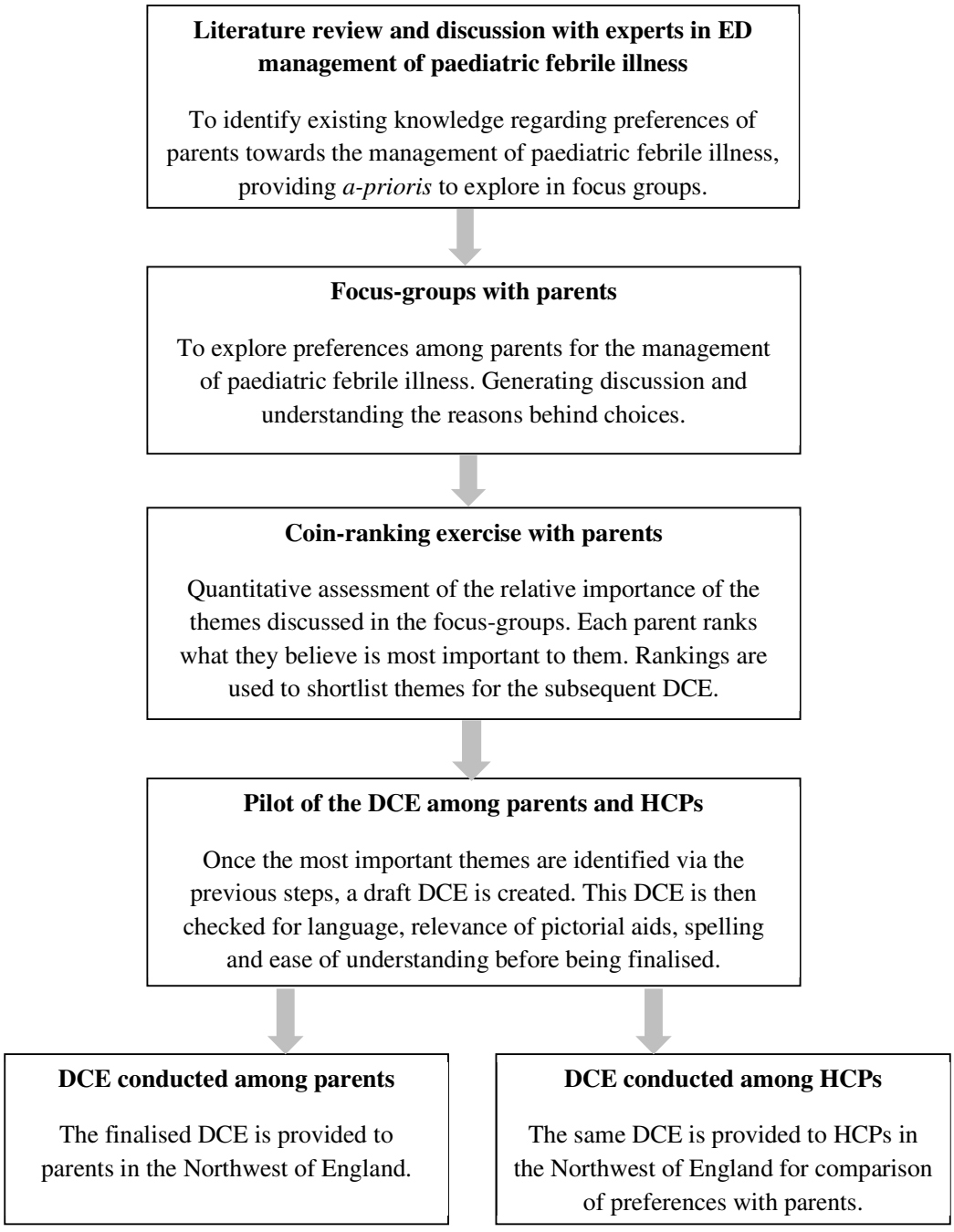
Materials & Methods

Multi-phase research to determine preferences for the management of paediatric febrile illness in the ED

We conducted a brief literature review, discussions with experts in infectious diseases, and an iterative series of focus-groups, coin-ranking exercises and discrete-choice surveys from June 2018, to January 2019. The aim of the research was to explore parental and HCP preferences for the management of paediatric febrile illness and estimate the likely impact the introduction of POC testing may have on each group. The design of each phase of the research was dependent upon the findings from the previous phase, making the process as agile and patient-centric as possible. As the outputs from the research were planned to be used within a subsequent health economic model, we followed methodological guidelines from the International Society for Pharmacoeconomics and Outcomes Research (Hauber, et al. 2016) in designing the research. This involved a multi-phase iterative process of identifying attributes of potential importance through a literature review, the search criteria for which are provided in Table 15. This was followed by discussion with experts in paediatric infectious diseases, historical observational data (Leigh, Grant, et al. 2018) and a series of focus-groups. The findings from each of these previous sub-studies then culminated in a DCE, as shown in Figure 11. This methodology of starting with qualitative research (focus-groups or one-to-one interviews), which is then used to inform subsequent quantitative research, in the form of a DCE is considered good practice (Vass, Rigby and Payne 2017) (Bridges, et al. 2011) (Coast, et al. 2012), and

increasingly common within medical research (Wong, et al. 2014) (Shanahan, et al. 2019).

Figure 11: Iterative study flow for chapter 4



The study was approved by The Health and Life Sciences Research Committee at the University of Liverpool, reference number 3032. A copy of the ethical approval for this chapter is provided in Appendix 1. All participants consented to participation in writing after being provided with a participant information sheet and having had the opportunity to ask questions. Demographic information, for all respondents was collected immediately following consent.

Table 15: Search criteria for HCP and parental preferences literature review

MEDLINE Search: Searched 27th May 2018			
1	Febrile	**28**	ED
2	Pyrexial	**29**	Emergency services
3	Pyrexic	**30**	Emergency unit
4	Raised temperature	**31**	Accident and emergency
5	Fever	**32**	Accident & emergency
6	Feverish	**33**	Emergency room
7	High temperature	**34**	ER
8	Pyrexial	**35**	***OR/ 27-34***
9	Hyperthermia	**36**	Preference
10	***OR/ 1-10***	**37**	Discrete choice
11	Paediatric	**38**	DCE
12	Pediatric	**39**	Conjoint
13	Children	**40**	Part Worth
14	Child	**41**	Contingent valuation
15	Neonate	**42**	Satisfaction

16	Neonatal	**43**	Utility
17	Perinate	**53**	***OR/ 36-43***
18	Perinatal	**54**	***AND/ 10, 26, 35, 53***
19	Infant		
20	Toddler		
21	Adolescent		
22	Baby		
23	Babies		
24	Teenager		
25	Teenage		
26	***OR/ 11-25***		
27	Emergency department		

Phase 1: Focus group discussions with parents

Qualitative research is increasingly advocated in the field of health economics (Corbin and Strauss 2008) (Hsieh and Shannon 2005). Some academics have made specific recommendations for the application of qualitative research methods alongside DCEs, paying particular attention to the identification of attributes and levels (Louviere, Flynn and Carson 2010) (Naik-Panvelkar, Armour and Saini 2013).

Focus groups have been widely used in health research in recent years to explore the perspectives of patients and other groups in the health care system (van Dongen, et al. 2017) (Jarab, et al. 2018), including within emergency care (Grant, et al. 2016) (Swallmeh, Byers and Arisha 2018). Focus groups are often included in mixed-

methods studies to gain more information on how to construct questionnaires or interpret results. The fact that the group process helps people to identify and clarify their views is considered to be an important advantage of focus-groups compared with individual interviews (Kitzinger 1995). We believed this to be particularly useful due to the potential for recall bias (some parents would have gone many years since their child last had a fever). Additionally, the group functions as a promoter of synergy and spontaneity, by encouraging the participants to comment, explain, disagree, and share often contrasting views (Tausch and Menold 2016). Therefore, experiences may be shared and opinions voiced, that might not have been mentioned during individual interviews (Carey, 1994; Stewart, Shamdasani, & Rook, 2007). This was an opinion shared by the social anthropologist guiding this part of the research within this chapter, who highlighted that one-to-one interviews, while providing an ability to delve deeper into specific subjects from a singular perspective, would not afford the same opportunity for debate, validation and exploration of differences in preferences. As we sought a multi-perspective discussion of the many potential areas of importance within the management of paediatric febrile illness, a focus-group design provided the best opportunity to address all relevant themes in sufficient depth and allow participants to be challenged on their views.

There were also several logistical benefits to using focus-groups rather than one-to-one interviews with this particular participant group. Parents were often, but not always, caring for their children while taking part in the discussions, changing nappies, feeding, changing clothes and observing children to ensure they were safe. This ensured that we maximised the number of parents able to take part by removing the

need for childcare prior to taking part, which may have acted as a barrier to participation. A focus group dynamic enabled participants to drop in and out where necessary and pass on the conversation to the next parent. Given the frequency of interruption for the majority of parents talking part, this provided a natural segue for beliefs and experiences to be discussed from alternative perspectives. In the event of a one-to-one interview, it was envisaged that conversation may become more staccato and that any flow of conversation, themes and ideas may be lost as a result of frequent distraction.

Focus group recruitment

Representatives from all proposed study sites were provided the same information (provided in Appendix 2), before agreeing to take part or decline in hosting (or allowing the use of their premises) for the focus-group discussions. This comprised a brief phone conversation with the representatives from each site, and the provision of a poster to provide a study overview and discuss the aims of the project. In all but one location (a pub in Chorley Lancashire, which was home to a men's darts team), a gatekeeper approach was used, a requirement in all cases in order to gain access to the respondents.

As the majority of respondents were recruited in local government coordinated children's centres, this approach was deemed the most appropriate in order to safeguard the parents (and their children), and prevent parents being put under any unanticipated pressure if asked without prior warning if they wished to participate in

the focus groups. Representatives from locations where gatekeeping measures were in place mentioned the focus-groups to prospective participants between one and two weeks prior to the planned focus-group dates. This provided a large window for respondents to discuss the study with their friends and family, decide whether it was right for them and ultimately to reconsider or decide not to take part. This was an important requirement in the cases of the children's centres that were used to facilitate focus-groups, as the rooms used were often very small play rooms. If parents did not wish to take part, we did not want to immerse them in the experience by having the focus-groups take place 'around' them, and clearly single out those not willing or able to take part. In all locations where a gatekeeper was involved, the representative from the organisation was present throughout the focus-group discussions, but other than introducing the researcher, remained uninvolved other than observing throughout the focus-groups.

Initially, eight focus-groups took place with parents of children aged <11 years, in six locations across the North-West of England, between June and July 2018. In order to obtain a breadth of respondents of varying demographics and with children of varying ages, the strategy for recruiting to the focus-groups was iterative, predominantly based on the demographics of previous respondents, enabling imbalances in participant characteristics to be addressed in order to ensure more balanced sampling. The first focus-groups took place in two children's centres following consultation with Liverpool City Council and representatives from several Liverpool-based Sure Start centres. Sure Start is a UK Government area-based initiative, announced in 1998 by the then Chancellor of the Exchequer, Gordon Brown, applying primarily in England,

which gives help and advice on child and family health, parenting, money, training and employment. Some centres also provide early learning and play centres. Sure Start centres provide childcare, typically for younger children, providing an opportunity to speak to parents of infants and younger children while their children were present. One Sure Start centre was located in an area considered more disadvantaged, with a large Somali community, while the other was in a less disadvantaged area, associated with young professionals and students, and located close to the neighbouring University. Three focus-groups were conducted across these two Sure Start centres (two in the more disadvantaged area and one in the less disadvantaged). We subsequently conducted three further focus-groups, the first of which taking place at a spinning class in Brighouse, West Yorkshire, where respondents were typically older, of higher socioeconomic status, and with children aged 6-11. A subsequent focus-group of parents of varying ages and socioeconomic status, and with children of varying ages was performed at a parent teacher association in Euxton, Lancashire. One final focus group took place among a men's darts team, which consisted of younger men of varying socioeconomic status from Chorley, Lancashire.

How were the focus groups conducted?

Before commencing the focus-groups, the study was explained in full by the researcher, with reference to the participant information leaflet (Appendix 3). This provided respondents the opportunity to leave. Finally, before commencing the focus-groups, respondents were invited to ask questions about the study. At this point a consent form was provided, and once signed the focus-groups commenced.

Participants were also asked to keep their participant information leaflet, as these provided contact details for the principal researcher of the study, where any concerns with the study could be raised. A copy of the consent form is provided in Appendix 4. All focus-groups were audio-recorded and subsequently transcribed with the permission of the parents taking part. All participants in the focus-groups received a box of chocolates as a thank you for their participation.

The mean focus-group size was 4-5 people (range 3-7), with a mean duration of 27.4 minutes, (range 18-46 minutes). Focus-groups were moderated by the principal researcher, and observed by staff from each venue, who were familiar with the participant groups, with the exception of the single focus group that took place with a men's darts team in a pub. The group sessions were comfortable discussions among respondents who may have known or had pre-existing relationships with other respondents in the groups. During five of the eight focus-groups, children aged less than 12 months were also present during the discussion, usually playing with toys, as shown in Figure 12.

Figure 12: Focus-group in a soft-play centre

With reference to a topic guide, respondents were invited to discuss any theme they considered relevant to the management of fever in children, with a focus on themes identified during the initial literature review, namely: waiting times, preferred HCPs, staying overnight, having many tests, pain from investigations, antibiotics and time waiting to receive updates.

Phase 2: Coin-ranking exercises with parents

Following the focus groups, respondents were asked to rank which of the themes discussed during the focus-groups were of most importance to them, to explore the importance of each theme.

The aims of this exercise were two-fold, the first of which was to supplement responses from the participants. This was particularly true of the more reflective participants who were perhaps less comfortable with immediate verbal responses, and

who needed additional time for thinking and to consider all of the themes under consideration, as discussed elsewhere (Colucci 2007). Given the high level of diversity within the focus-groups, and the fact that many of the participants did not have English as a first language, this also provided another means of articulating their preferences. The second aim of the coin-ranking exercise was to make comparative analysis of the relative importance of all the themes discussed possible. Bloor and colleagues have previously reported on the utility of such exercises in focusing the attention of the group on the core topic of the study (Bloor, et al. 2001). Given that the primary aim of the focus-groups was to gain a level of understanding regarding what matters most to parents when their child is in the ED with a fever, the ranking exercise enabled participants to consider all the previous points raised in combination, and then distil this down into what really mattered to them. This ranking information, when combined for all participants would then be used to short list themes to include in the DCE, ensuring that only those which were most important were included.

How were the coin-ranking exercises conducted?

All participants taking part in the eight focus groups were invited to take part in coin-ranking exercises once the focus-groups had come to an end. When piloted during the first focus group, respondents were provided with printed labels (one for each theme in the topic guide, plus several blanks to add in new themes which may have been discovered during the focus group), and asked to rank these in a ladder from most to least important, as observed in previous studies (Marino 2008) (Brownbill, Braunack-Mayer and Miller 2020).

Following the pilot ranking exercise conducted during the first focus-group and discussion with the social anthropologist guiding this section of the research, it was clear that absolute, but not relative preferences could be identified, with some respondents preferring to place two or more labels on the same rung of the ladder, as they could not decide between them in terms of ranked importance. As a result, following this pilot of the ranking exercise, the methodology was amended as per suggestions from the supervisory team, with participants instead provided with 100 penny coins, as observed in previous studies using tokens instead (Gneezy, Imas and Jaroszewicz 2020) (Gneezy and Potters 1997). Respondents were asked to assign the coins to the attributes/labels they believed were most important, as demonstrated in Figure 13. If only one theme was of absolute importance to the respondent, all 100 coins would be assigned to this theme, if something was in no way important, zero coins would be attributed. Coins were chosen as the means of demonstrating relative preferences as they provided a clear visual depiction of relative value, with the label with the most coins being the most important. This also limited the level of arithmetic required, making the process more accessible and less prone to mathematical error. If for example the coins were not physically present, but hypothetical, this would have required repeated subtractions from 100 to determine how many intangible coins respondents had remaining, and then repeating this process if changes were to be made. One disadvantage of this method was that children who were often present would occasionally knock over, mix up or remove coins from piles. In these cases, parents repeated the exercise. Once participants had distributed their coins to the labels representing the themes covered during the focus groups and were happy with their

decisions, the researcher present during the exercise manually counted the number of coins in each pile, storing this information in a Microsoft Excel spreadsheet on a tablet computer.

Figure 13: Coin-ranking exercise

Phase 3: Discrete-choice experiment with parents and HCPs

The final phase of designing our research into the preferences for the management of paediatric febrile illness in the ED was to construct a DCE. DCE methodology is well described (Tinelli, Ryan and Bond 2016) (Soekhai, et al. 2019), and used extensively to measure patients' preferences for healthcare services, for everything from side-effects of medications, to care planning and diagnostics. DCEs have a long history in preference research, and have been used successfully not only in healthcare but also marketing (Dellaert, Donkers and Soest 2012), transportation (Saleh and Farrell 2005) (Devarasetty, Burris and Shaw 2012), housing (Hoshino 2011), and environment research (Fimereli and Mourato 2013) (Campbell 2007). To date, most healthcare-related research concerning DCEs has taken place in the context of planned care (Farrar, et al. 2000) and chronic diseases, with use of DCEs in an ED-context limited to date. This provided the opportunity for a novel application of this methodology.

In DCEs, respondents are given a hypothetical scenario typically comparing one option to one or more others, and asked to choose which of the available options they prefer. The discrete choice experiment is founded in random utility theory (RUT), which plays a key role in the understanding and interpretation of the behavioural processes examined in the DCE. Because DCE methodology has its theoretical foundation in random utility theory, it therefore relies on the assumptions of economic rationality and utility maximization (von Neumann and Morgenstern 1944). In stating a preference, for example choosing one option over another, the individual is assumed to choose the alternative that yields their highest individual benefit, known as utility.

Moreover, the utility yielded by an alternative is assumed to depend solely on the utilities associated with its composing attributes and attribute levels (Lancaster 1966). In other words, a good or service can be characterised by a set of attributes and levels, and it is these bundles of attributes and levels that respondents are choosing between, not the named options themselves. It is the previous steps of performing a brief literature review, consultation with experts in infectious diseases, focus groups and coin-ranking exercises, which decided what these attributes should be.

DCEs are used to determine the significance of the attributes that describe the goods or service and the extent to which individuals are willing to trade one attribute for another (Drummond, et al. 1997). Information on the relative importance of the selected attributes can be useful for those involved in policy decisions, service planning and those setting resource allocation priorities, and may be designed with that in mind (Baltussen and Niessen 2006).

When presented with the opportunity to choose between one or more options, the process of choosing must be repeated with the values (levels) of the characteristics (attributes) changing each time. This ensures sufficient variability and enables the estimation of each part-worth utility for each level of every attribute. The attributes used for our DCE are listed in Table 16, with levels determined from responses obtained during the focus-groups and previously published data from our hospital (Leigh, Grant, et al. 2018). The DCE was provided to participants using both paper forms and a tablet-PC. An example survey question is provided in Figure 14. A pictorial design was used for the DCE, as observed in previous studies (Lange, Hehl-Lange and Brewer 2007), to aid understanding and minimise cognitive burden. We

expected respondents to be of varying academic, cultural and geographical backgrounds, and whilst we mandated that respondents could read English, we wished to minimise the need to be fluent or highly literate, where possible, to maximise the likelihood of completion.

Table 16: Attributes and levels of the Discrete Choice Experiment

Attribute	**Levels**
HCP treating child	Doctor in postgraduate training*
	Nurse practitioner
	Consultant#
Pain experienced from investigations	Low
	Moderate
Likelihood of receiving antibiotics	Low (7%)
	Moderate (20%)
	High (33%)
Total time in the ED	1 hour,
	2 hours
	3 hours,
	4 hours
Out-of-pocket cost to parent/guardian#	£7 (~$9)
	£12 (~$16)
	£20 (~$26)
Receive rapid point of care test during triage	Yes,
	No

**Doctor in postgraduate training is defined as a medically qualified doctor, between grades of foundation Year 1 and 2 (intern in the USA) and registrar (resident in the USA). # Consultant (UK) is equivalent to an attending physician in the USA.*
 # As healthcare is free at the point of use within NHS hospitals, such costs were stated to be out-of-pocket, covering things such as transport to and from the ED, parking and food while on site.

Figure 14: DCE survey example

	OPTION A	OPTION B
MANAGING THE CHILD	 CONSULTANT	 NURSE PRACTITIONER
PAIN OR DISCOMFORT EXPERIENCED BY CHILD FROM INVESTIGATIONS	 LOW	 MODERATE
LIKELIHOOD OF CHILD RECEIVING ANTIBIOTICS	 HIGH	 LOW
PERSONAL COST TO PARENT OF CHILD	 £7	 £20
TOTAL TIME SPENT IN EMERGENCY DEPT. BY CHILD	 4 HOURS	 1 HOUR
USE A DIAGNOSTIC POINT-OF-CARE TEST AT TRIAGE?		
I CHOOSE ...	☐	☐

In order to capture the preferences of all stakeholders involved during the management of paediatric febrile illness in the ED, our DCE was provided to two groups of respondents: (1) HCPs working in a children's ED and (2), parents recruited from children's soft play centres who had not previously taken part in the focus-groups that preceded the DCE. HCPs had not previously been involved in the study up until this point as we wished for the study to be patient/parent-centric in design. It was important

that we first sought the opinions of parents, understood what really mattered to this group, and compare and contrast views on these themes between parents and HCPs.

How did we recruit parents into the DCE?

We consecutively invited parents of children aged 0-11 years who were proficient in reading English. We recruited parents in play centres not under the management of local government, from Liverpool and Lancashire, ensuring these were in different locations to the Sure Start centres we performed the initial focus-groups and ranking exercises in. This was to ensure that our estimation (planning of the DCE), and validation sources (responses to the DCE) did not overlap. In total five soft play centres were visited a total of ten times (approximately two visits per centre). The researcher sat in the soft play centre and consecutively approached parents/carers to take part in the DCE. At this point a participant information leaflet was provided and prospective respondents were left alone to consider whether they would like to take part. After a period of approximately 5 to 10 minutes, the researcher asked if the parents would like to take part in the study, at which point a consent form would be provided. Parents who participated would be left alone with a tablet computer or paper forms to complete the DCE, with the researcher close by in the event of questions. In situations where multiple parents were present in a group, parents were asked not to confer and to answer the DCE alone, in order to prevent the possibility for a group dynamic to affect reporting, where all parents within the group would provide near similar answers based on pre-agreed themes of importance.

How did we recruit HCPs into the DCE?

For HCPs completing the DCE, we included qualified nursing and medical staff of all grades with experience of managing febrile children, working within our tertiary care specialist hospital located in the North West of England. The researcher attended the ED thirteen times in total at varying times. Initially recruitment was conducted during the hours of 9am to 5pm, however it was quickly apparent that HCPs were too busy to commit the time to answer the DCE during this busy period. In some cases, HCPs started the DCE but would then be away for up to 30 minutes in consultation with patients and writing up notes. As a result, it was decided that attending the ED out of hours would be preferable. Following discussion with the on-site nurse consultant, it was recommended that we recruit HCPs into the DCE around the time of 'handover', where some staff were at the end of their shifts and replacement staff were also on site ready to take over responsibility. We attended the ED three hours before handover and immediately informed all HCPs in the ED of the study, providing participant information leaflets. This gave HCPs plenty of time to consider the study and decide if they wished to participate. We then consecutively asked HCPs whether they would like to take part in the study, provided consent forms, and recruited HCPs to conduct the DCE using a tablet computer or paper forms.

The DCE design

Each respondent, whether a parent or HCP received 14 discrete-choice tasks plus two tests of rationality, one as the first task, to gauge understanding, and one as the final

task, to measure sustained concentration. A test of rationality was deemed essential as DCEs are based on stated-choice theory, and with this, responses are assumed to be rational, that is, conforming to the axioms of completeness, transitivity and monotonicity (more is better). A typical test of rationality, or 'dominance test' involves providing a choice between two alternatives, where one alternative is clearly superior, for example, less pain, less costs, lower waiting times. The use of such tests has become commonplace in applied DCEs, hence our inclusion of this component (Tervonen, et al. 2018). Respondents who choose what is considered to be the 'irrational' option, are then assumed either to be irrational, to not be paying attention, or to not have understood the task. Failing either test of rationality led to responses being excluded from analysis as performed in previous studies (Chen, Cheng and Zhang 2015) (de Vries, de Vries and Dekker 2015) (Finkelstein, Bilger and Flynn 2015) (Gelhorn, Poon and Davies 2015).

Ngene was used to develop the DCE survey and assess for level balance, the syntax for which is provided in Appendix 5. Respondents chose between two scenarios for managing paediatric febrile illness, characterised by differing levels of the attributes included (Figure 12). No opt-out option was included as this was deemed unrealistic in children's emergency care. The options were not labelled, and simply listed as choice A and choice B. The reason for this was that both parents, and particularly HCPs may have had prior beliefs about the value of diagnostic innovation. Had we labelled one option as 'novel' or 'new' there was a chance that respondents would all things being equal, choose this option more than the alternative, irrespective of the attributes and levels under consideration. This phenomenon has been observed in

several studies, where the inclusion of labels has appeared to play a significant role in individual choices but reduced the attention respondents give to the attributes themselves (Jin, et al. 2017) (de Bekker-Grob, et al. 2010). As a result, unlabelled DCEs may be more suitable to investigate trade-offs between attributes and for respondents who do not have familiarity with the alternative labels.

Finally, as the full factorial experiment would have required (3^3 x 2^2 x 4^1 = 432) choices per respondent, (where every mutually exclusive combination of attribute levels was compared against all other feasible alternatives), a D-optimal design was chosen with two blocks. The order choice tasks were presented was randomised using a random number generator, with the randomisation of question order resulting in 100 differentially ordered DCE booklets. The reason for randomising the order DCE choice sets were answered was to minimise the likelihood of survey fatigue, or a lack of concentration, disproportionately affecting a subset of questions, thereby biasing results. Literature suggests that a drop in concentration often occurs at the end of longer surveys (Egleston, Miller and Meropol 2011). As such, randomising question/choice set order was hoped to mitigate against any systemic biases which may arise as a result. A selection of surveys were pilot tested with ten parents and five HCPs not involved in the main study; each using a booklet with mutually exclusive and randomly ordered questions. This was done to gauge interpretation and response times; during which period a researcher was available to answer any questions.

Although sample-size calculations represent a technical challenge in DCEs, we used a parametric approach (Louviere, Hensher and Swait 2000) to determine the sample-size, equal to 48 respondents in total, or 24 per group, as demonstrated in Figure 15.

Figure 15: Sample-size calculation for DCE

$$N \geq \frac{1-p}{Tp(a^2)} \left[\Phi^{-1} \left(\frac{1+\alpha}{2} \right) \right]^2$$

Where:

N = Sample size

P = Expected choice proportion (i.e. 50% if two choices to pick from, 33.3% if three choices, 25% if four choices)

T = Number of choice tasks performed by each respondent

α = Confidence level (i.e. 95%, 99%)

a = accuracy level (i.e. observed proportion within 10% of true one)

Φ^{-1} *= Inverse normal distribution*

N > {(1-0.5)/[(14*0.5)*(0.9*0.9)]}*{NORM.S.INV*[(1+0.95)/2]^2}

N > 24

Reference: (Louviere, Hensher and Swait 2000)

DCE data analysis

Given the heterogeneity observed within the focus groups and coin ranking exercises, we used a mixed-logit model to estimate parental and HCP preferences for the management of paediatric febrile illness. Mixed logit allows for the possibility that the preferences and choices of each respondent represent a random 'draw' from a

distribution of preferences among the wider population. As such, this method incorporates the inclusion and quantification of unobserved preference heterogeneity, and therefore allows for interpersonal differences based on slight variations in what people believe are most important. This methodology has become a gold-standard within DCE literature (Eberth, et al. 2009), allowing the estimation of not just point estimates, but additionally estimates of uncertainty, expressed in terms of both standard deviations and 95% confidence intervals.

Effects coding was used for all categorical variables. In both effects coding and dummy-variable coding, each non-omitted attribute level is assigned a value of 1 when that level is present in the corresponding profile and 0 when another non-omitted level is present in the corresponding profile. The only difference between the two coding methods is related to the coding of the non-omitted levels when the omitted level is present in the profile. With effects coding (also known as deviation contrast, or ANOVA coding) all non-omitted levels are coded as –1 when the omitted level is present. With dummy variable coding, all non-omitted levels are coded as 0 when the omitted level is present. The coefficient on the omitted level of an effects-coded variable can thus be recovered as the negative sum of the coefficients on the non-omitted levels of that attribute. Therefore, effects coding yields a unique coefficient for each attribute level included in the study, and therefore guarantees that preference weights for all of the levels of a categorical variable sum to zero. This was developed out of the desire to test all category means as deviations against one overall mean value, or the 'grand mean' of all values under consideration. By doing so one avoids preselecting a (potentially arbitrary) reference category as in dummy coding.

Finally, to account for observed heterogeneity in preferences among our sample, including parents having different views on management by nurse practitioners or doctors; or additionally, doctors having different views on waiting times to nurses, it was assumed that population preferences for all effects-coded variables followed a normal distribution. As such, each individual preference observed constituted a random draw from this population distribution. Waiting times and costs were coded as linear continuous variables. We first estimated a main-effects model, and subsequently estimated sub-group effects, which for parents, were determined from the focus-group exercise, and included variables such as parent age, child age and the number of children a parent had. Due to a lack of qualitative research with HCPs prior to the DCE, sub-group analyses of HCP preferences were determined by the clinical lead for the chapter and the primary supervisor of this thesis.

Willingness-to-pay (WTP) and willingness-to-wait (WTW) analyses were performed to determine how respondents were willing to trade off one attribute for another, for example, prolonging waiting times in order to be managed by a more experienced clinician. These trade-offs are commonplace within DCE literature (Bethge 2009) (Hauber, et al. 2016), and we followed recommended methods from the International Society for Pharmacoeconomics and Outcomes Research (Johnson, et al. 2013) in determining these trade-offs, or 'marginal rates of substitution'. As such, confidence intervals for WTP and WTW estimates were estimated via joint-distributed bootstrapping, with all analyses performed using Stata 14 (StataCorp LP) and deemed statistically significant at the conventional 5% level.

Results

Characteristics of participants focus-groups (Phase 1)

Fifty parents were invited to participate in the focus-groups, forty-two of whom accepted. Characteristics of those taking part in the focus-groups are provided in Table 17. Most respondents were female (92.9%) and aged between 26 and 45 (90.5%), with 66.6% of the group receiving some form of higher education and 71.4% in full-time employment. Most parents had one (52.4%), or two (38.1%) children. Approximately 64% of the group had experienced a fever among one or more of their children in the past 6 months and 35.7% had previously taken their child to the ED with a fever.

Table 17: Baseline characteristics of those completing focus groups

Attribute	**n**	**%**
Age		
16-20	0	0.0%
21-25	1	2.4%
26-35	23	54.8%
36-45	15	35.7%
46-55	3	7.1%
56+	0	0.0%
Female		
Yes	39	92.9%
No	3	7.1%
Number of children		
1	22	52.4%
2	16	38.1%
3	3	7.1%
4	1	2.4%
5+	0	0.0%
Educational status		
High school	1	2.4%
College/vocational	12	28.6%
University/higher education	19	45.2%
Masters/Postgraduate	9	21.4%
Professional degree	0	0.0%

Doctorate	0	0.0%
Employment status		
Full time	30	71.4%
Part time	6	14.3%
Unemployed/looking for work	3	7.1%
Unemployed/not looking for work	0	0.0%
Student	1	2.4%
Retired	0	0.0%
Self employed	2	4.8%
Annual Household income		
<£15,000	6	14.3%
£15,001-£40,000	15	35.7%
£40,001-£60,000	15	35.7%
£60,001+	6	14.3%
Last time their child had a fever		
<3 months	19	45.2%
3-6 months	8	19.0%
6-12 months	4	9.5%
1-2 years	4	9.5%
2+ years	7	16.7%
Ever taken their child to the ED?		
Yes	31	73.8%
No	11	26.2%
Ever taken their child to the ED with fever?		
Yes	15	35.7%
No	27	64.3%

Findings from focus-groups (phase 1): What matters when your child has febrile illness?

Theme 1: Feelings of concern & anxiety, and the desire for communication

There was agreement among the parent participants that fever in their children caused significant concern and anxiety. Observable symptoms such as a high temperature, and factors such as the age of the child combined with their knowledge of serious

illnesses made their decision to visit the ED more likely. This mother with two young children described her reaction to her personal 'emergency':

"I know if I did take him you're taking him 'cause you feel personally that it's an emergency… I'm thinking this is serious because this is a temperature so high… But he was tiny and erm you know, you read so much about sort of erm there's so much flying around like meningitis" **Mother of two children, varied SES group**

These concerns were more prominent among less experienced, or new parents who lacked experience of nursing young children and were concerned that they might miss life-threatening symptoms. This father described how if 'you'd been there before' you would know what you were doing, suggesting that prior experience was for him, a critical factor to increase his confidence to manage childhood fevers:

I'm not that concerned now she's a little bit more robust but because she was that bit younger, it was a bit more worrying… maybe if you had a couple of kids and you'd been there before and you think you know it's just the way it is er it's a bit more accepting but I think with your first definitely it makes you a bit more anxious. **Father of one child, varied SES group**

This fear was more pronounced the younger the child was with this same father mentioning infants being unable to communicate verbally as a primary cause of worry:

It's the uncertainty it's the fact that they you don't really know what's wrong with them, do you, with a young child? It's not like they can tell you. If a young child's got a fever it's going to bring about more worry **Father of one child, varied SES group**

There was also a general agreement that improved communication and healthcare providers providing consistent updates, particularly that children were not

unknowingly deteriorating, would provide significant benefit to both more experienced and new parents.

"We're sat waiting thinking, is this getting worse and worse and worse? Especially when it's kind of told that's a danger sign if they're [temperature is] *over 40"* **Mother of two children, high SES group**

While parents appreciated that health care workers were very busy with more urgent cases, even a few words from a staff member to tell them that they had not been forgotten would have made all the difference to their experience of waiting:

I understand they've got to see more children and obviously erm it all depends on what the circumstances are for other children as well and they do have an emergencies and stuff but I'd rather them come out and say oh by the way, and just keep in contact" **New Mother, low SES group**

The length of the 'wait' in the ED seemed to increase parental anxiety, despite being a clinical setting and knowing that assistance (if needed) would be immediate. This mother described how regular reassurance would have helped alleviate her anxiety and made the wait more bearable:

"Actually, I was kept waiting for a very, very long time and erm without anybody actually reassuring me that this little baby was actually going to be ok". M**other of two children, varied SES group**

If regular updates were not possible, this mother believed that more could be done to reassure parents and carers at the time of booking in, to alleviate worry and set the expectation that the long wait was a positive sign that their case had not been deemed urgent:

"You just want somebody to say we're sorry you're waiting but we're not, if we were worried, we'd rush you through" **Mother of one child, low SES group**

Additionally, parents expressed collective discomfort with what they believed to be 'bothering' or interrupting staff if they perceived their time waiting in the ED to be excessive, or if they believed they had been forgotten. Specifically, there was a strong aversion to being seen to be ignoring the reality that other, perhaps more acutely ill, children, may need treatment first:

"Yeah, cause I felt like I went over to the triage saying how long, how long? But they do have an emergencies and stuff you know? Like I know, I understand they've got to see more children and obviously, erm, it all depends on what the circumstances are for other children as well" **Mother of one, low SES group**

Parents were concerned that they would be perceived as 'difficult' or 'demanding' if they asked for news but couldn't work out how else they would get information. This mother describes watching successive parents ask ('nag') staff about their children, but as no information was shared with them, felt they would have to ask themselves to find out:

"You could see the desk clerk as well was being like, ending up being like, sort of ending up feeling nagged the whole time. You see about 20 people going up asking, and I was going in and saying, ' I understand I'm not more important than anyone else I'm just looking to know sort of roughly **Mother of two, high SES group**

Theme 2: Beliefs regarding waiting times

There was a consistency among respondents that reduced waiting times would be beneficial to parents and children alike. Parents did not articulate this as a wish to avoid the inconvenience of waiting, but to the ways in which wait times increased their feelings of anxiety and affected their children's wellbeing. Parental concerns about the wait centered around three key themes, the first of which was their concern about the disruption to usual sleep and feeding routine for the child. Often parents were alone in the ED, unable to use their mobile phones without leaving the ED, and many had not come prepared for such a long wait and could not work out how to buy the resources they needed, or even call for a friend or relative to bring them:

"I felt really anxious because I realised that I only had one bottle for her and she's on a special milk as it is, so it wasn't like I can just go and get those premade beautiful bottles at the supermarket and then I was freaking out she's due for a feed soon… and I was by myself too. So I was starting to get anxious going, I've been waiting, I don't know how long I've got more to go, can I go out? Can I even call someone? **Mother of one, low SES group**

Parents were also concerned about the possibility of catching conditions from other children in the ED which may be contagious. Waiting areas were not segregated and the number of cases meant that parents and children were often sitting in close proximity to one another for prolonged periods:

"… and they said we don't know how long it's going to be 'cause she wasn't obviously urgent, so we left 'cause it was just they couldn't give us an answer and we'd already been there for two hours and we just weighed it up thinking we felt like she was probably going to catch something from a poorly child and make herself, make her iller erm" **Mother of one, low SES group**

The third concern for parents was the difficulty in having to regulate the number of times they or their children leave the waiting room to go to the toilet or obtain drinks.

"I think you feel very trapped in the waiting room, you can't go anywhere you could be sat there for three hours and you're nervous to go anywhere even go to the toilet." **Mother of one, high SES group**

While all parents agreed that prolonged waiting times caused some degree of anxiety, those with a higher socioeconomic status, and those with greater levels of employment also voiced disutility towards the process of waiting itself. This may represent a proxy for 'opportunity cost', the cost of the next best alternative forgone. Parents with higher levels of employment and a higher economic 'value' of their time, may be less inclined to spend extensive periods of time waiting for results.

"I suppose in A&E its always the speed isn't it its always the speed of the thing, you get in there and you go an hour or four hours wait and you're like ah but they don't tell you that when you get there do they, you see the four hours sign and you think ah god you know" **Mother of two, high SES group**

In contrast, this mother from a low SES group described how she would be prepared to wait for a very long time if she believed that her child was seriously ill:

"I think if you're going to a hospital for something so severe then I think to me waiting that long is you know you've just got to wait that long so to me it's like I would wait if they said wait a day, or whatever I would sit in that waiting room and wait" **Female, Low SES group**

This last example highlights the importance of regular and frank communication and rapid diagnosis in the ED. If parents knew that their child was seriously ill, then they

would wait patiently for treatment for many hours. They would also wait for long periods if they were given regular updates, and assurances that if they visited the shop for drinks or the lavatory, they would not be forgotten. If they were reassured that their child was well, they would leave and undertake the nursing at home to ensure that the seriously ill children could be treated.

Theme 3: Parental perceptions of the need for, and use of, antibiotics for fever in children

Parents did not express a desire for their children to be given antibiotics for fever, reaffirming their belief that if they were required, they would be provided by the clinician, underlining the ideas that 'the doctor knows best'. Many parents seemed aware that children should not be given antibiotics too often, and that they might not 'work' for fever:

"I would be happy with that [being checked by a clinician], *they're the experienced people, do you know what I mean? I trust their decision and you don't want them to have too many antibiotics, do you? Yeah as long as someone's seen her and checked her over, I wouldn't mind if she didn't get them"* **Mother of two, varied SES group**

What parents wanted was for their child to be 'checked over' by a doctor or nurse so that they could be reassured that the fever was mild and could be treated with fluids, rest and with a mild analgesic if needed:

"Yeah as long as someone's seen her and checked her over I wouldn't mind if she didn't get them (04.41) she's fine" **Mother of one, high SES group**

This feeling was reiterated with parents not wanting their children to take anything which provided limited clinical benefit, with parents demonstrating awareness of the potential side-effects of antibiotics*:*

"Just because you do get side effects, (like diarrhoea), you don't want to take something that's not worth it" **Mother of two, high SES group**

There were however instances where parents (typically older, with older children), believed that antibiotics provided 'security', however this was a rare opinion among the 42 parents in the seven focus groups:

Interviewer: In the case of a fever, so you took your child in for a fever, how do you feel about receiving/not receiving antibiotics?

R1: Always antibiotics, makes you feel better (laughs)

Interviewer: why does it make you feel better?

R1: 'Cause it's a security thing, even though you're going the doctors it's like antibiotics will not do that but I think when it's your children when its yourself you know that you can work out you know in a few months or whatever but with your child it can be so long until things get out of their systems so you just think oh antibiotics

R2: It's that happy medium isn't it?

R1: I am definitely for them just because I think they cure the issue in my opinion

Interviewer: What if I told you that only about 5-8% of all fevers are bacterial in nature would you still want them?

R1: Erm, I would yeah, I totally know what you're saying but if it's the thought of it could give them something quite simple like an antibiotic and it would get rid of it.

High SES group

To summarise the findings on the theme of parental perceptions regarding the use of antibiotics; the evidence collected strongly suggests that drivers for antibiotics are not coming from parents. Additionally, among those who do desire antibiotics, and in some cases, with a strong preference, these parents appear poorly informed and therefore open to persuasion or the provision of evidence that they may not be needed. This reiterates the importance of communication and the value that rapid assessment and the provision of information may provide.

Theme 4: Does the experience of the treating healthcare professional matter, or is it being seen that counts?

Parents were generally impartial about who treated their child when attending the ED with fever, as there was confidence among respondents that all HCPs who may treat their child would have sufficient qualifications, experience and expertise to do so:

"You're just relieved to be seen by anyone, they've not just come in off the street and gone to uni for one day have they" **Mother of two, High SES group**

This theme was observed across all ages and SES groups, with respondents across most of the focus-groups believing that if less experienced nursing staff or doctors were unsure, they would consult with a more experienced clinician for reassurance:

"But you know that they are still talking to the consultants" **Mother of one, low SES group**

"No, I don't think it would bother me 'cause obviously, if it was something that they couldn't deal with hopefully they'd go and find somebody" **Mother of three, varied SES group**

Additionally, some of the parents interviewed exhibited a clear preference for less experienced doctors, based on the belief that they may be able to interact with children easier due to being younger:

"Yeah I mean possibly as well I'm quite happy if it was a junior doctor as they might be able to interact with my kids just a bit easier on that level, than somebody that's like a lot older and thinks they're wiser and knows more" **Mother of two, high SES group**

Additionally, others believed that medical training would still be 'fresh' in their minds, and therefore they would be more likely to follow clinical guidelines and err on the side of caution due to their lack of experience. This was in contrast to more experienced clinicians, including consultants, who respondents believed may have become "blasé" or "complacent" and not give their case the attention it deserved and miss a critical symptom:

"So you know, they've ticked more boxes than somebody who's been doing it for 40 years do you know the person that's been doing it for 40 years I don't know in my opinion can become a bit blasé and think they know what's happening before they've even assessed the person properly whereas the junior ones obviously tick through everything that they're meant to go through" **Father of one, varied SES group**

To have a clinician who established a rapport with themselves and their child, and who would seek advice was clearly valued by parents as the best option for the initial assessment:

I think a newly qualified doctor would mean everything's fresh and I think what you tend to find with new, newly qualified people or new professions is a bit more cautious and they will err on the side of caution because of the lack of experience. So, they will perhaps seek

advice or perhaps whereas a doctor with experience would go well actually I've seen this over time as a new doctor wouldn't and they'd err on the side of caution." **Mother of one, high SES group**

There were however clear exceptions to this, with respondents suggesting that if they believed the condition was something more serious, they would like to see a specialist, in this case either a registrar or a consultant:

"I think if it was like you were going in with an emergency and you know something quite common erm I think you'd want to see anyone where I think maybe if your child had like a lot of problems you might want to see someone specialised." **Mother of two, low SES group.**

To summarise, parents were generally impartial about who treated their child when attending the ED with fever, as there was confidence among respondents that all HCPs who may treat their child would have sufficient qualifications, experience and expertise to do so. Parents could see the benefits of treatment by less experienced clinicians, including shorter wait times and a perceived reduced level of complacency. This is important as with the use of assistive technologies for the diagnosis of infectious diseases in the ED, including POC testing, it can be expected that less experienced clinicians may attend more cases that would otherwise be overseen by registrars or consultants, as confidence to withhold antibiotics increases. However, in the event that parents perceive a more serious condition, a strong preference for more experienced clinicians remained, highlighting the importance of trust in clinical decision making, and the parental anxiety inherent to febrile illness.

Theme 5: The role of Point of Care (POC) testing

Parents understood the rationale for testing their children well, re-iterating that which tests were provided was predominantly based on the symptomology of the child at the time. When discussing the potential role of universal POC testing however, there was concern that in the event of a negative finding, this would negate the need for follow-up with a clinician.

"Just for reassurance and I think as X was saying before you're taking them to Alder Hey because you know that there's an issue there you're not just taking them the doctors you know there is something more and you want them checking over" **Mother of one, low SES group**

Not being seen or checked adequately was a recurring concern for parents, who wanted to be sure that if they were sent home, everything had been properly explored and checked, and that this had been explained to them adequately so that they would not feel the need to return:

Cause I feel a lot of the time, especially when I go to walk in centres, it's just a viral go home I feel sometimes they just they don't examine the child fully and they just use that as oh its fine just send them home and then I end up back in the walk in centre or A&E again with the same symptoms" **Mother of one, High SES group**

Given that many parents had to wait so long to be seen, to finish with a comparatively brief consultation of five minutes without further investigation, was concerning to parents:

It's a bit of anti-climax isn't it just you know 5 minutes to say this is a common this or it's a common that whereas the test could give you a bit more in depth" **Father of one, varied SES group**

Parents explained their reasoning why they might prefer POC-testing, suggesting that tangible evidence and explanation and communication of the reasons why children are being discharged or admitted was important.

"I would feel much happier because they've actually took the time to take the blood test, whether that was a finger prick rather than just saying, going in oh it's just a viral go home" **Mother of two, varied SES group**

This was founded in a lack of assurance when clinical teams use the term, 'Oh it's just viral', which parents reported as common during previous experiences with fever in their children.

"I don't know it sounds daft but something physical to say, 'This is what it is'. Not just a nurse relaying it going, 'Yeah its viral.. er this, this, this make them rest', something physical so you can sort of dilute the information yourself as opposed to somebody telling you" **Father of one, varied SES group**

Parents wanted a named diagnosis, confirmed with a test, so that they could go away and perhaps research it themselves and could reassure themselves that the symptoms that they had observed in their child, were consistent with the wider information:

"I suppose it would be more of a comfort with more of a concrete answer I suppose, rather than just it's a virus go and rest at home, an actual blood test result would bring me more reassurance" **Mother of two, high SES group**

To summarise, the findings related to this theme suggest strongly that parents want to go away with 'something' - some token (physical or intangible) that they have been 'seen' and 'heard' and that gives them what they need to go away and feel reassured. This may be antibiotics, which may fuel antibiotic overprescribing, or simply information, so that they could perhaps research it themselves and reassure themselves that the symptoms that they had observed in their child, were consistent with the wider information. Given the many anxieties experienced by parents of children presenting to the ED with febrile illness, including a perception of not being heard, or their child not being examined "adequately", or for a sufficiently long period of time, it is clear that POC testing which may provide results far sooner, would assuage many concerns, thereby reducing the likelihood of return visits. It is this characteristic of POC testing, the option to provide tangible evidence and explanation and communicate the reasons why children are being discharged or admitted which was most valuable to parents.

Quantitative findings: Prioritising what matters using a coin-ranking exercise (phase 2)

All parents who took part in the focus-group exercises agreed to take part in the subsequent ranking exercises. Table 18 demonstrates the results of our coin-ranking exercise which immediately followed the focus-group discussions, with Figures 16 and 17 showing two of the coin-ranking exercises taking place. Respondents demonstrated a clear preference for minimising the amount of time waiting for updates about their child's condition, a theme which strongly featured in the focus-groups and

was almost unanimously viewed as essential to improving satisfaction with care. This was then followed by minimising waiting times/total time in the ED, minimising pain and discomfort from diagnostic tests where possible and being seen by a more experienced clinician. Finally, despite literature suggesting that parents often request or seek antibiotics, a finding which was also observed in a small number of participants within the focus-groups; being provided with antibiotics was least important to parents, in addition to having to stay overnight in the hospital.

Table 18: Results of coin-ranking exercise

All	**Total**	**Mean**	**Median**	**Max**	**Min**	**Range**
Reducing the amount of time waiting for updates about your child	616	26.8	25	75	0	75
Spending less time in A&E	393	17.1	20	48	0	48
Minimising pain/discomfort due to tests	322	14.0	12	40	0	40
Being seen by a more experienced doctor	314	13.7	10	42	0	42
Having lots of tests to rule out different causes	300	13.0	12	32	0	32
Not having to stay overnight in the hospital	149	6.5	0	25	0	25
Being given antibiotics	119	5.2	5	20	0	20

Figure 16: Coin-ranking exercise following focus-group

Figure 17: Coin-ranking exercise at soft-play centre

When taking account of the heterogeneity in the groups interviewed, we observed differences in the coin-ranking exercise which deviated from the pooled estimates provided in Table 18, suggesting indicative differences in preferences for different groups. Figure 18 highlights normalised preferences from the coin-ranking exercise for those in the lower SES group, with Figure 19 providing comparative pooled estimates utilising all observations. These figures highlight that receiving more tests and being managed by a clinician with greater experience were most important to lower SES groups, while waiting times were the least important, as was staying overnight. Although based on a relatively small sample set of 40 individuals, when compared to the pooled sample of all responses in Figure 19, these findings suggest an indicative (although by no means definitive) difference in preferences which may be affected by SES.

Figure 18: Normalised preferences: Low SES

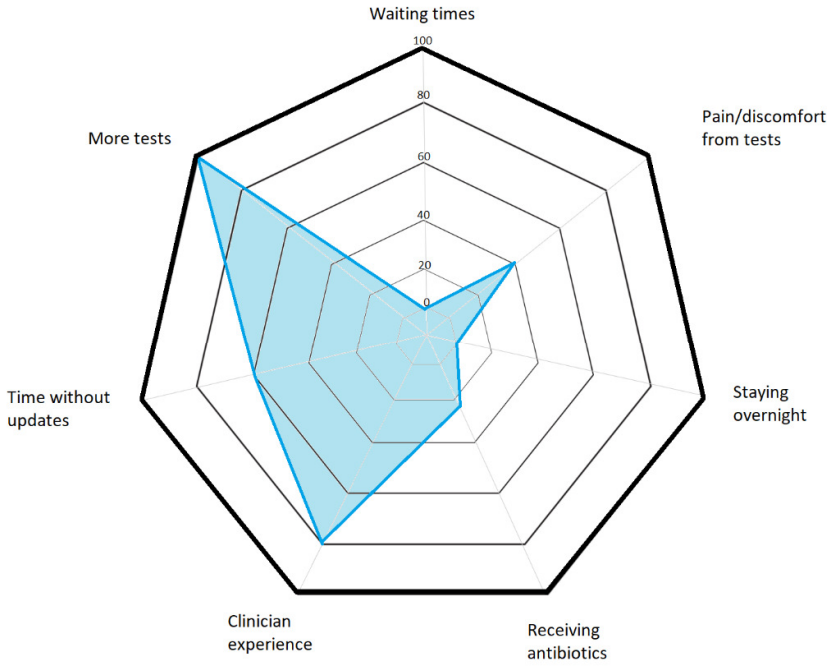
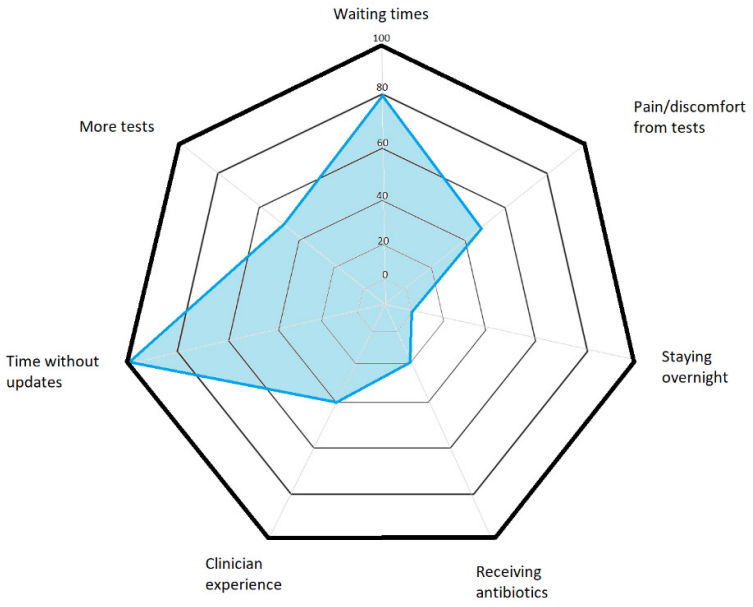
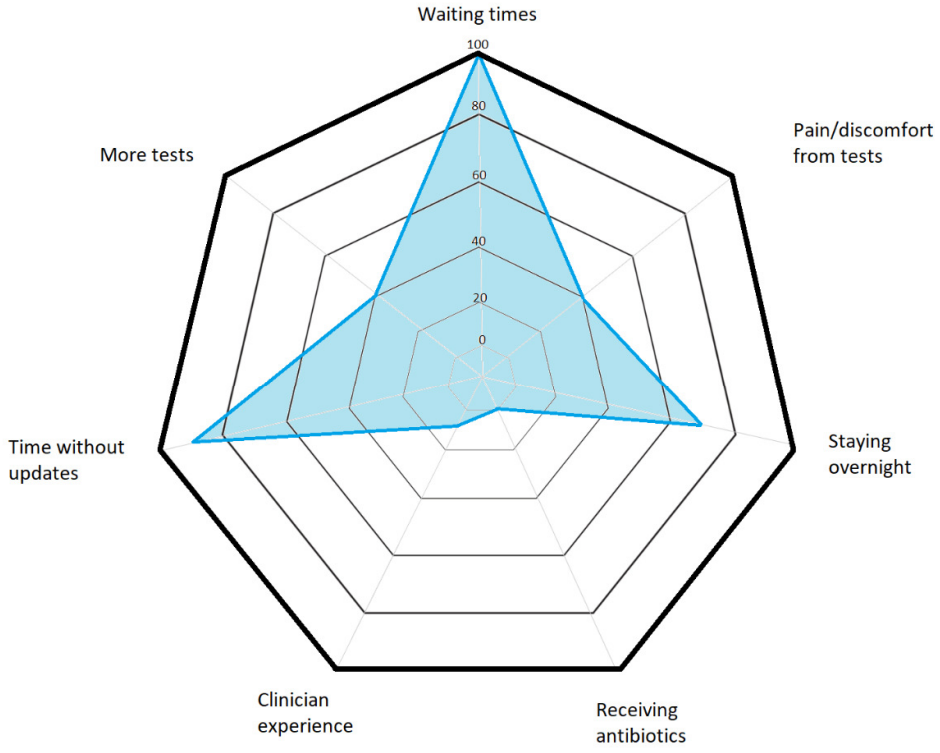


Figure 19: Normalised preferences: Pooled observations



Conversely, Figure 20 demonstrates normalised preferences for those in the higher educational status and higher SES group; where waiting times were the most important, followed by time without updates and staying overnight. Unlike the lower SES group, receiving more tests and being managed by a clinician with greater experience were not valued significantly.

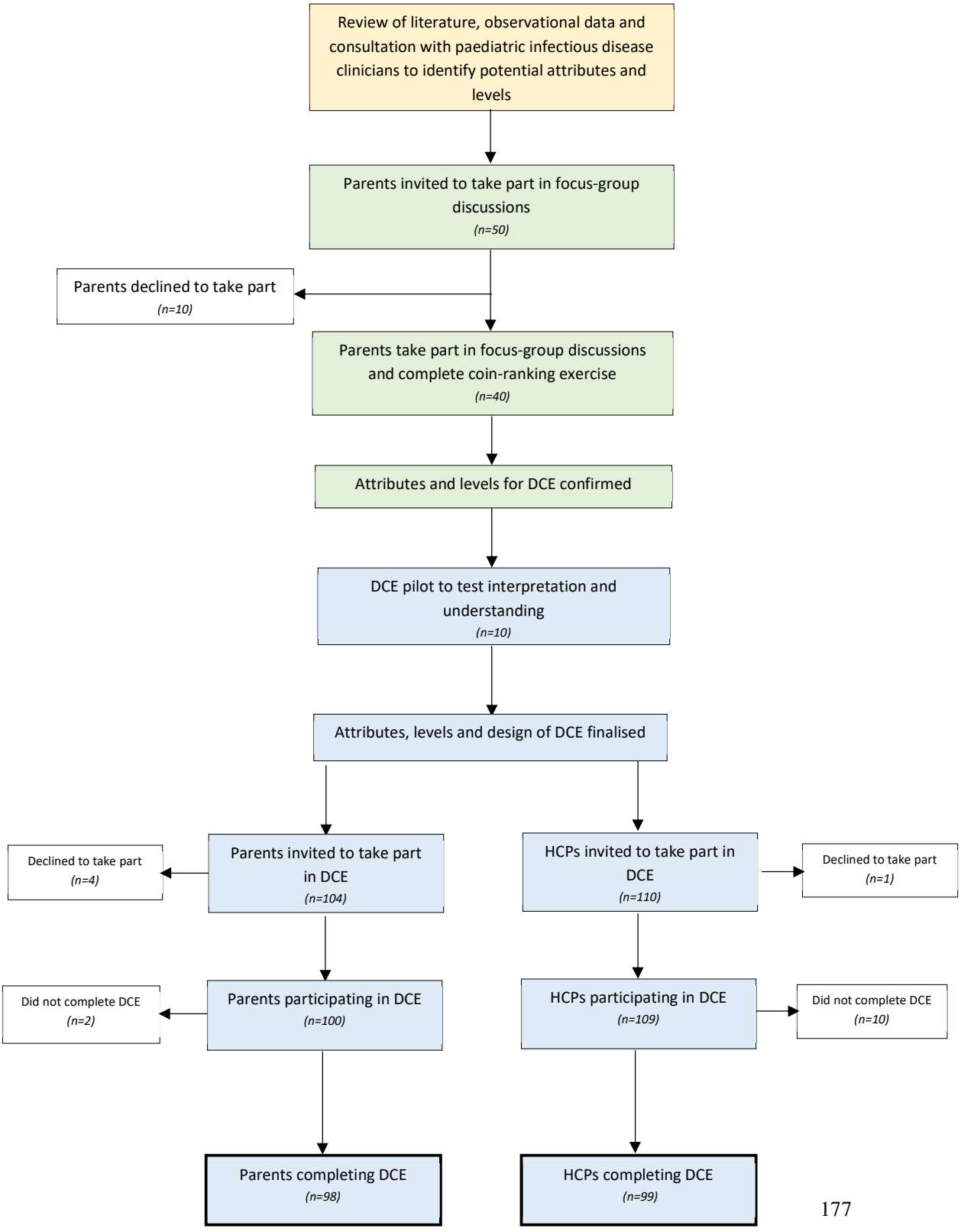
Figure 20: Normalised preferences, high SES



Characteristics of participants: Discrete-choice experiment (phase 3)

The remaining 104 parents and 101 HCPs who did not take part in either the focus-groups or coin-ranking exercise, were invited to take part in the DCE. Two parents and one HCP did not complete the DCE, and four parents and one HCP declined to take part, leaving a total of 98 parents and 99 HCPs, (Figure 21).

Figure 21: Flow diagram of study phases



No one failed either of the tests of rationality, resulting in a 100% understanding rate. Tables 19 and 20 illustrate the demographics of those completing the DCE in the parental and HCP cohorts, respectively.

Table 19: Characteristics of parents completing the DCE

CHARACTERISTICS OF PARENTS		
Age (years)	Percentage	Number
21-25	9.1%	9
26-35	48.5%	48
36-45	33.3%	33
46-55	5.1%	5
Prefer Not to Say	2.0%	2
Gender		
Female	78.6%	77
Male	21.4%	21
Educational Status		
High School	9.1%	9
College	28.3%	28
University	33.3%	33
Masters	13.1%	13
Professional	4.0%	4
Doctorate	6.0%	6
Other	1.0%	1
Prefer Not to Say	3.0%	3
Annual Household Income		
<£25,000	35.4%	35
£25,001-£40,000	21.2%	21
£40,001-£80,000	31.2%	31
>£80,000	8.1%	8
Prefer Not to Say	16.2%	16
Where would you go first if your child had a fever?		
Pharmacy	14.1%	14
Walk in Centre	14.1%	14
General Practitioner	37.4%	37
NHS 111*	25.2%	25
Emergency department	2.0%	2
None of the Above	5.1%	5
Characteristics of children		
Age of youngest child	Percentage	Number

<1 year	38.3%	38
1-3 years	34.4%	34
4-6 years	12.1%	12
7-10 years	12.1%	12
11+years	1.0%	1
Age of oldest child		
<1 year	24.2%	24
1-3 years	23.3%	23
4-6 years	21.2%	21
7-10 years	15.2%	15
11+years	14.1%	14
Number of children		
1	47.5%	47
2	35.4%	35
3	11.1%	11
4	0.0%	0
5+	2.0%	2
Last time any of your children had a fever?		
<3 months	14.1%	14
3-6 months	14.1%	14
7-12months	37.4%	37
1-2 years	25.2%	25
2+ years	2.0%	2
None of the Above	5.1%	5

**NHS 111 is a telephone service for if you have an urgent medical problem and you are unsure what to do.*

Table 20: Characteristics of HCPs completing the DCE

CHARACTERISTICS OF HCPs		
Age (years)	Percentage	Number
21-25	8.1%	8
26-35	57.6%	57
36-45	20.2%	20
46-55	11.1%	11
56+	3%	3
Prefer Not to Say	0.0%	0
Years of experience as a HCP		
<5 years	41.4%	41
6-10 years	28.3%	28
11-15 years	14.1%	14
16-20 years	7.1%	7
21+ years	9.1%	9
Experience working with children		
<5 years	43.4%	43
6-10 years	25.3%	25
11-15 years	14.1%	14
16-20 years	8.1%	8
21+ years	9.1%	9
Clinical grade		
Healthcare Assistant	10.1%	10
Staff Nurse	28.3%	28
Senior staff nurse/Sister	19.2%	19
ST1/2	12.1%	12
ST3/4	23.2%	23
Nurse practitioner	4%	4
Consultant	3%	3

**ST-/4 (UK) is the equivalent of a 1st-4th year resident in the USA. Consultant (UK) is equivalent to an attending physician in the USA.*

Parental and HCP preferences for the management of febrile illness using a DCE (phase 3)

We took the most important attributes when managing paediatric febrile illness in the ED, as judged by parents during the focus-groups and coin-ranking exercises and

created a discrete-choice experiment based around these attributes. In the DCE, 5/6 attributes for parents and 6/6 attributes for HCPs were statistically significant, suggesting importance with respect to the management of paediatric febrile illness. Table 21 illustrates preferences for each characteristic. Pain/discomfort associated with investigations, and total time in the ED were associated with significant dissatisfaction in both the parental and HCP groups. For HCPs, providing a POC test during triage, which may provide diagnostic information earlier, was associated with significantly increased satisfaction with care provided. Parents exhibited no preferences for receiving antibiotics, suggesting this is not a meaningful influencer of satisfaction with care in this group. However, for HCPs, a high likelihood of receiving antibiotics was associated with significant disutility. Finally, treatment by doctors in postgraduate training reduced satisfaction with care amongst both the HCP and parent groups.

Table 21: Preferences in the management of paediatric febrile illness of parents and HCPs

	Parents (n=98)			HCPs (n=99)		
	Coefficient	95% Confidence Interval		Coefficient	95% Confidence Interval	
Staff grade						
Trainee doctor	-0.244*	-0.472	-0.016	-0.204*	-0.398	-0.099
Nurse Practitioner	-0.135	-0.368	0.098	0.081*	-0.106	0.27
Consultant (reference group)	0.379	N/A#		0.032	N/A#	
Likelihood of receiving antibiotics						
Low (reference group)	0.143	N/A#		0.729	N/A#	
Medium	0.031	-0.865	0.803	-0.111	-0.594	0.371
High	-0.174	-0.74	0.392	-0.618*	-1.0	-0.236
Moderate pain from investigations (relative to low)	-0.462*	-0.613	-0.312	-0.439*	-0.558	-0.32
Receive POC test during triage (relative to no)	0.627*	0.484	0.769	0.723*	0.562	0.884
Total time spent in the ED (per hour)	-0.608*	-0.78	-0.435	-0.679*	-0.81	-0.548
Out-of-pocket cost to parents (per £1)	-0.036*	-0.065	-0.007	-0.051*	-0.074	-0.028
Observations	2,772			2,774		
Log likelihood	-722.1			-674.8		

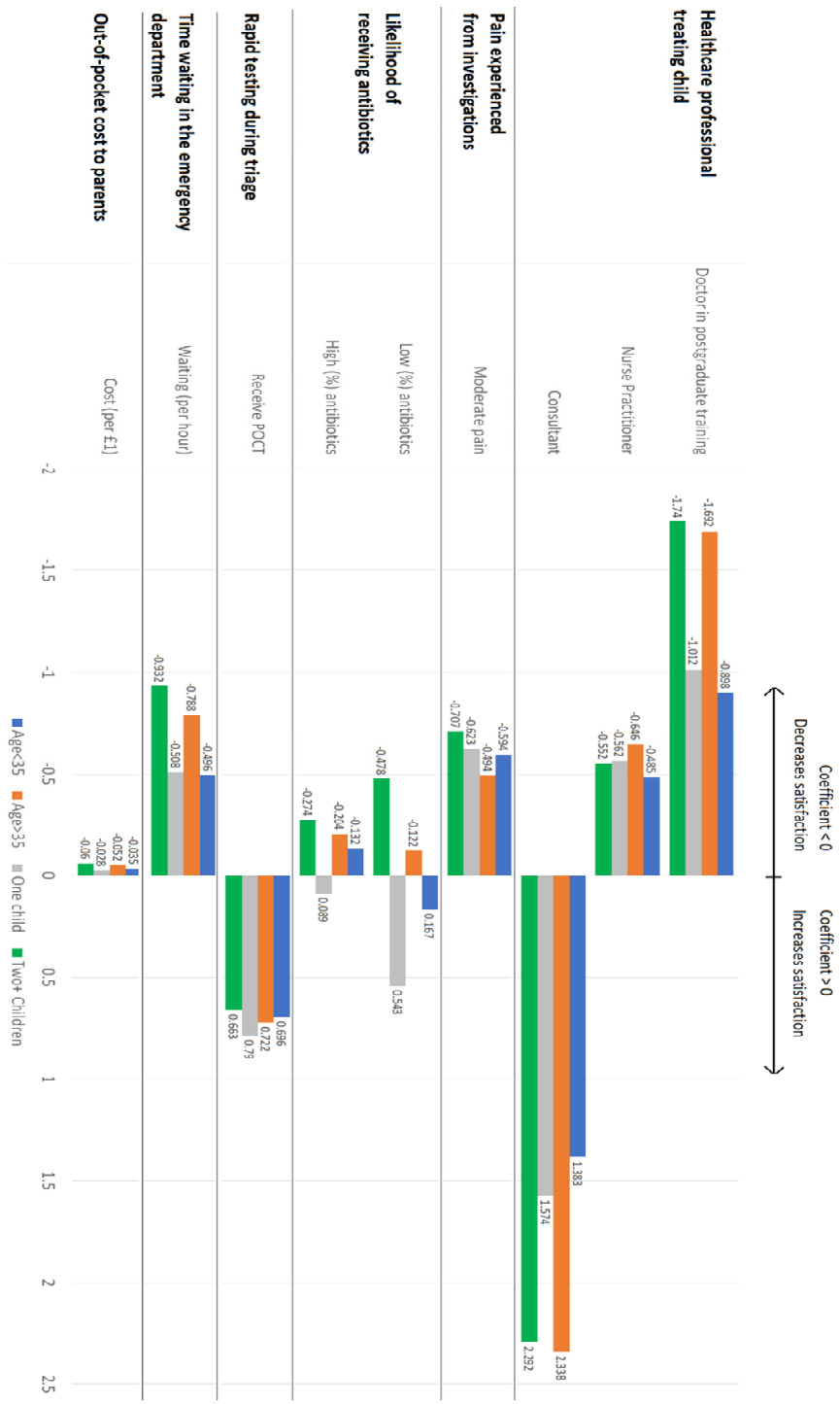
**Significant at 5% level. Table represents β coefficients and confidence intervals from multinomial conditional logit regression. The regression coefficients for each attribute level represents the mean part-worth utility of that attribute level in the respondent sample. A positive value denotes utility/satisfaction and a negative value denotes disutility/dissatisfaction.*
 # Reference group for which a 95% confidence interval cannot be calculated in a mixed logit regression

Differences in parents' and HCP's preferences for the management of paediatric febrile illness

Reducing pain from investigations was important among all parent and HCP groups, as was receiving a rapid test during triage. Parents with more than 1 child and those aged >35 years displayed significantly stronger preferences for minimising visit time

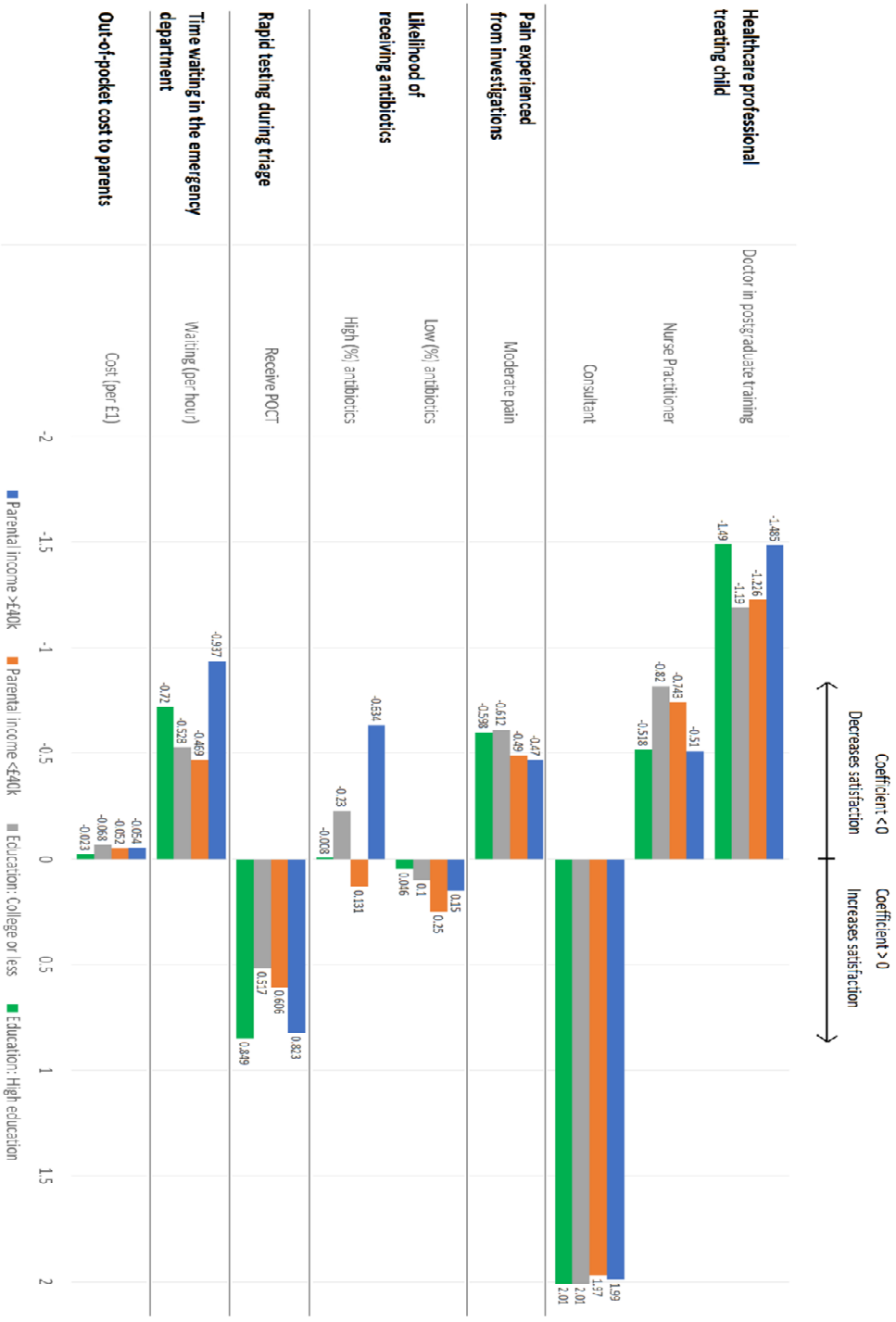
and receiving consultant-led care, than those with fewer one child and those aged <35 years, as demonstrated in Figure 22.

Figure 22: Preferences exhibited by parents; stratified by parents age and number of children



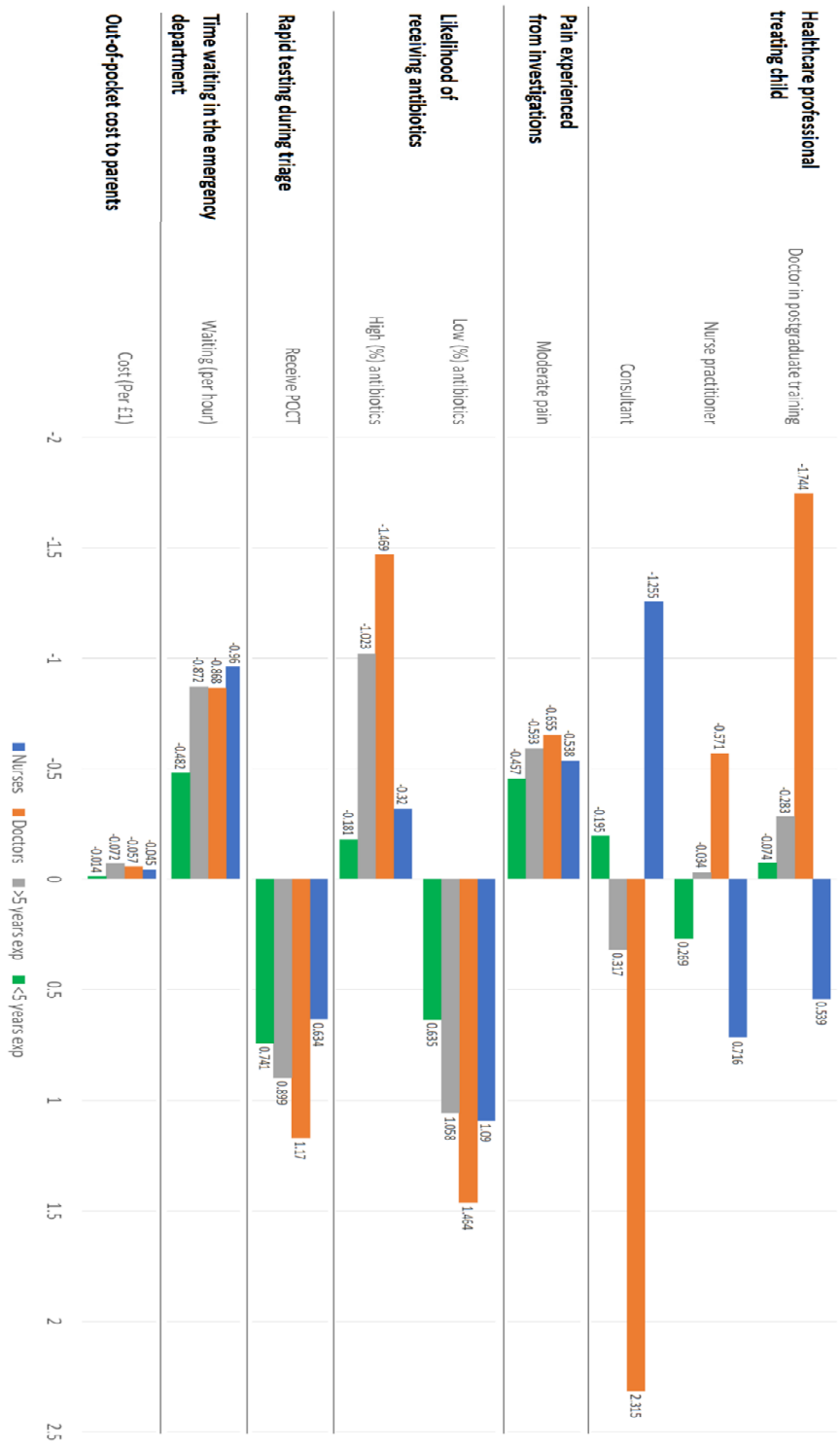
Parents educated to college level or lower, were less concerned about being managed by a doctor in postgraduate training than those having completed higher education, as shown in Figure 23.

Figure 23: Preferences exhibited by parents; stratified by educational status and annual household income



A moderate to high probability of receiving antibiotics reduced satisfaction among those educated to University level or higher, or with a household income of >£40,000 per year. Conversely, among those educated to college level or less, or with a household income of <£40,000 per year, receiving antibiotics did not affect utility. All HCP subgroups preferred not to prescribe antibiotics, but none more so than doctors, who also exhibited a stronger preference for rapid testing than nurses (Figure 24).

Figure 24: Variation in healthcare providers preferences for the management of paediatric febrile illness; stratified by experience and role



Trade-offs: Willingness-to-pay and willingness-to-wait

Parents were willing-to-pay £16.89 (95% CI £8.30 - £26.88) for a one-hour reduction in total visit time, increasing to £17.35 for those with an annual household income of more than £40,000, and decreasing to £9.02 for those with an annual household income of less than £40,000. Parents were also willing to pay £12.83 (95% CI £8.61 - £17.05) to avoid pain from diagnostic investigations, increasing to £14.70 for those with an annual household income of more than £40,000, and decreasing to £9.42 for those with an annual household income of less than £40,000. Parents were also willing-to-pay £6.77 (95% CI (-) £0.37 - £10.71) to see a consultant if the alternative was management by a doctor in postgraduate training. Parents expressed a WTW an additional 45.6 minutes, [95%CI (-)19.3mins–60.4mins] to avoid pain from investigations, increasing to 62.7 minutes for those with an annual household income of less than £40,000, and decreasing to 30.1 minutes for those with an annual household income of more than £40,000 (Figure 25). Parents were also willing to wait 24.1 minutes [95%CI (-)15.9mins–46.9mins] for management by a consultant, increasing to 37 minutes for those with an annual household income of less than £40,000, and decreasing to 18.3 minutes for those with an annual household income of more than £40,000 (Figure 26). Similarly, HCPs were willing to extend waiting times by 39.9 minutes [95%CI (-)30.9mins–79.5mins], provided it reduced the likelihood of prescribing antibiotics.

Figure 25: Willingness-to-pay, by socioeconomic status

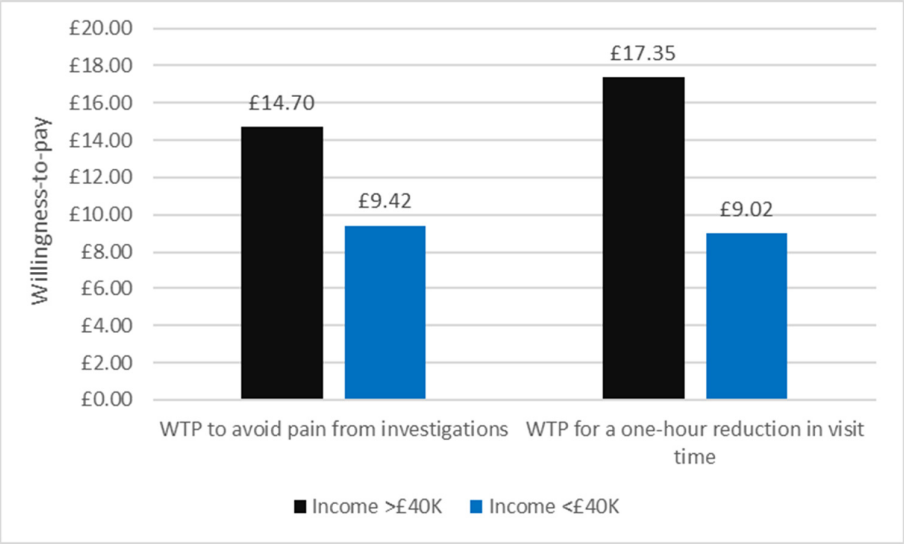
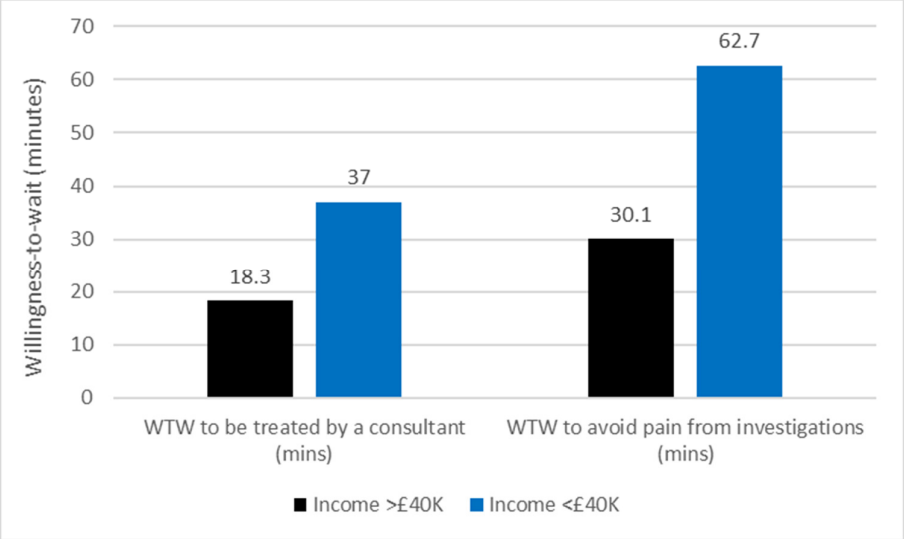


Figure 26: Willingness-to-wait, by socioeconomic status



Discussion

Summary of principal findings

Among a sample recruited from the Northwest of England, the findings of this chapter suggest that parents and HCPs are largely in agreement regarding what matters during

the management of paediatric febrile illness. This finding provides reassurance when considering the future implementation and acceptability of novel infectious disease diagnostics designed for implementation within EDs. Both HCPs and parents were most concerned about reducing ED visit time, receiving diagnostic information faster and avoiding pain from investigations. The strength of this preference was similar across subgroups of differing sociodemographic characteristics. The desire to reduce waiting times was borne not out of a desire for convenience, and minimising the time burden of ED attendance, but rather a desire to minimise anxiety and concern, with parents averse to long waiting times due to the possibility of their child deteriorating during this period. Parents also displayed strong preferences for being treated by consultants rather than doctors in postgraduate training, particularly when it was believed that their children were more acutely ill, or where the ability of children to communicate their symptoms (infants), was diminished. Finally, the likelihood of receiving antibiotics did not significantly influence satisfaction among parents, whereas for HCPs, this was a significant concern. Because the availability of diagnostics is increasing, with CRP-POC testing now used in some UK primary care settings (NICE 2014) (Butler, Gillespie and White 2019), the findings of this study may be used to prioritize the implementation of upcoming diagnostics, to best meet the preferences of both parents/carers and HCPs.

Strengths & limitations of the chapter

The strengths of this chapter include the iterative multi-phase process for determining attributes of importance. While it is strongly recommended that in-depth qualitative studies underpin quantitative research regarding preferences, this is rarely performed

in practice, with a recent systematic review highlighting that only 44% of identified DCEs in healthcare used qualitative methods (Vass, Rigby and Payne 2017). The use of qualitative methods which were central to the design of the DCE, provides reassurance that the choices under consideration (and the attributes therein), were likely to be of genuine importance to respondents. This in turn maximises the likelihood of the findings firstly being informative, and secondly being representative of underlying population level views. A second strength is the variety of sub-group analyses performed. It was apparent from the early-phase focus-groups and from existing literature, that views on several themes of importance, including the role of antibiotics and the experience of the treating clinician were likely to vary among participants. The use of sub-group analyses which took account of both known and plausible confounders, including socioeconomic status, age, and both parenting and clinical experience, enabled the identification of differential preferences among distinct sub-groups. These findings may inform future implementation of novel diagnostic modalities in the ED. A final strength is that this study is a first-of-its-kind in measuring preferences for the management of paediatric febrile illness. No study to date has previously explored the factors underpinning preferences and decision making for paediatric febrile illness in an ED setting, despite the high frequency of occurrence (Alpern and Henretig 2006).

The findings of this study should however also be viewed in the context of several limitations. Firstly, our parent population were sought from the community including playgroups, Sure Start centres and parent-teacher associations, rather than those presenting to the ED with fever. While this may be considered a strength in the context

of government funded healthcare systems, as the public effectively pays for the National Health Service (NHS), this may have affected the accuracy of our results due to recall bias, and may have disproportionately affected parents of older children, where the incidence of febrile illness is much lower than among infants. Secondly, the sample sizes in both the parental and HCP DCEs were limited, making robust, definitive conclusions, particularly among sub-groups, difficult. While the analysis did elude to differences in preferences, and more specifically, willingness-to-pay and willingness-to-wait estimations among those of differing socioeconomic status, the limitations of sub-group sample size mean that these remain hypothesis generating as opposed to definitive. Future research may aim to explore this potential difference in what matters to parents of differing socioeconomic status, when their child is in the ED with a fever. Additionally, the generalisability of our findings may also be limited by data collection being restricted to the North West of England. It is possible that preferences for the attributes considered may differ in other healthcare settings; and other locations, which may be characterised by different cultures, different beliefs and which may not benefit from having a highly renowned specialist paediatric hospital in their area. These factors were all not accounted for in our analysis. Finally, while every effort was made to ensure that the attributes chosen were important to parents and HCPs alike, we cannot be certain that the methods utilised led to an accurate representation of preferences, particularly during the early-stage qualitative phase. For example, while focus-groups were deemed beneficial over one-to-one interviews for several reasons, including promoting conversation, we could not account for the impact of pre-existing relationships and power dynamics. It is possible that dominant individuals were present who the researchers were not aware of. A regression to

consensus on the views of these dominant individuals may then have occurred unknowingly as a by-product of not wanting to challenge any existing hierarchy. Additionally, the need to use a gatekeeper approach in five of the six locations for the focus-groups may also have had an impact. Ethical dilemmas can occur if the gatekeeper is coercive in influencing participant involvement in the research (Singh and Wassenaar 2016). Similarly, denial of access if the gatekeeper selects potential respondents based on their relationship, rather than their ability to contribute to the research, is also an important consideration. A gatekeeper may have chosen similar respondents who they believed would have worked well together and agreed with one another, which may have come at the expense of losing breadth in opinions on the issues under consideration. Finally, although every effort was made to ensure we captured what mattered to parents and HCPs when managing paediatric febrile illness in the ED, we could not include every important variable. The ability of respondents to provide rational and consistent responses to a DCE is affected with each additional attribute included. Prior systematic reviews have shown that the average DCE in healthcare includes approximately 5.74 attributes (Trapero-Bertran, Rodríguez-Martín and López-Bastida 2019), similar to this chapter which included six. As a result, it is likely that factors which are influential in determining satisfaction with care (beyond those included) were omitted, an issue which future research should aim to address.

Interpretation considering other evidence

A systematic review of factors associated with satisfaction with care in emergency medicine highlighted that perceived waiting times, interpersonal skills, staff attitudes and both provision and explanation of information are most closely linked with

parental satisfaction with care (Taylor and Benger 2004). It is likely that as clinical experience increases, so too does confidence in decision making, meaning HCPs can provide greater reassurance, which along with parents equating experience with clinical acumen, may explain why consultant-led care was preferable. This may however have some important implications for the implementation of diagnostics in development. As familiarity with interpretation of diagnostics increases, and incorporation into clinical decision making becomes more routine, novel diagnostics may increase confidence among less experienced staff. This may result in these staff members being less likely to perform additional tests, less likely to prescribe antibiotics, to seek a second opinion from senior colleagues, and more confident in sending children home. While plausible in theory, it is important to state that the real-world evaluation of POC tests, and how they impact care pathways, is very much in its infancy (Verbakel, Turner, et al. 2017). Therefore, the suggestions made here should be considered hypothetical at best until rigorous studies provide more definitive evidence.

We identified a strong aversion from both parents and HCPs to children experiencing pain from investigations. While observational data suggest the likelihood of venepuncture during the management of paediatric febrile illness is low (Leigh, Grant, et al. 2018), pain from procedures including capillary blood sampling and venepuncture are often the most traumatic experience when a child's primary symptom is fever, impacting patient experience significantly (Postier, et al. 2018) (Friedrichsdorf, et al. 2018). Additionally, studies demonstrate that parents tend to overestimate pain experienced by their children (Chambers, Reid and Craig 1998)

(Jylli and Olsson 1995) (Kazak, Penati and Waibel 1995), and therefore our findings suggest that while pain from venepuncture may be expected to last a few minutes, pain from obtaining capillary blood from a finger prick for POC testing may be more favourable, thereby improving the experiences for both parents and children.

While substantial literature regarding the management of febrile illness suggests antibiotics are commonly sought by parents (Voepel-Lewis, Malviya and Tait 2005) (Huang, et al. 2007) (Nash, et al. 2002) (Alili-Idrizi, Dauti and Malaj 2014), we did not observe this trend. HCPs demonstrated a strong preference for avoiding antibiotic use where possible, likely a result of increased awareness of the growing threat of AMR; however, parents were indifferent to antibiotic use. This may be explained in part by increased efforts to educate the general population, with television programmes such as 'Trust me I'm a doctor', and Public Health England's 'keep antibiotics working' jingle being just two examples. As such, any novel diagnostics which provide diagnostic information within the window in which precautionary antibiotics are usually considered, are likely to improve not only HCP satisfaction, but also patient outcomes resulting from reduced AMR.

Chapter 4 summary

The aim of this chapter was to follow up on the findings of the previous, which demonstrated a clear economic value of improved febrile diagnostics; and determine whether healthcare providers and parents alike would also "value" any potential improvements in diagnostics. This chapter, reports for the first time, on what matters to parents and healthcare providers alike when managing paediatric febrile illness,

using an iterative approach. Utilising a combination of focus-groups with parents from various locations in Northern England, and a novel coin-ranking exercise, this chapter has provided deep qualitative insights regarding the themes most important to parents of febrile children, when they are being cared for in the ED. Using these findings, a first-of-its-kind discrete-choice experiment was then conducted with both parents and HCPs, to determine the comparative importance of various attributes of existing care pathways. The peer-reviewed published version of this chapter can be found in Appendix 6 below.

The findings of this chapter highlighted that both parents and HCPs feel strongly about the avoidance of pain and achieving a faster diagnosis in the context of managing paediatric febrile illness; but they are willing to trade these off against each other. While HCPs care strongly about reducing the use of antibiotics where possible, this does not affect decision making for parents, who demonstrated an indifference to antibiotic prescription. Finally, both HCPs and parents cared strongly about reducing ED visit time. The reasons for this strong preference to minimise ED visit times were several, with the focus-groups highlighting that time spent in the ED correlates strongly with anxiety and fear of deterioration. Taking the findings of this chapter as a whole, any advances in diagnostic capabilities, which may reduce waiting times and provide vital and much desired diagnostic information more promptly are likely to be of significant benefit. Furthermore, any technology which can reduce over-reliance on potentially avoidable invasive investigations and antibiotics can also be expected to improve both child and carer experience, and HCP satisfaction with care. The findings of this chapter therefore suggest that all things being equal, the addition of POC testing

or other diagnostic innovations within the ED is likely to improve both child and carer experience and HCP utility considerably.

This thesis has so far focused on ED management of paediatric febrile illness. However, given that an increasing number of ED attendances are non-urgent, including in the case of paediatric febrile illness, they may also be amenable to treatment in primary care. As such, one of the key recommendations of the Royal College of Emergency Medicine is to co-locate primary care services within ED settings (RCEM 2014). While there is limited evidence, reported benefits of introducing GPs in EDs for managing non-urgent cases, include reduced waiting times (Goodman, Gordon and Martin 2014) (Smith, et al. 2018), and reductions in invasive examinations (Khangura, Flodgren and Perera 2012). Based on the findings of this chapter and the previous chapters, this may provide another means of not only improving satisfaction with care for paediatric febrile illness, but also economic outcomes. The aim of the next chapter is to build upon the previous chapters and assess the impact that ED co-location of a primary care service may have on waiting times, admissions, antibiotic prescribing rates and healthcare costs. In doing so, it will be possible to explore the cost-effectiveness of ED co-location of GP services, for non-urgent presentations, including instances of paediatric febrile illness.

Chapter 4 Appendix

Appendix 1 – Ethical approval for DCE

Health and Life Sciences Research Ethics Committee (Human participants, tissues and databases)

13 April 2018

Dear Prof Carrol

I am pleased to inform you that your application for research ethics approval has been approved. Application details and conditions of approval can be found below. Appendix A contains a list of documents approved by the Committee. **Application Details**

Reference:	3032
Project Title:	Treating children with fever: What matters to parents and doctors
Principal Investigator/Supervisor:	Prof Enitan Carrol
Co-Investigator(s):	Mr Simon Leigh, Prof Louis Niessen
Lead Student Investigator:	-
Department:	Clinical Infection, Microbiology and Immunology
Approval Date:	13/04/2018
Approval Expiry Date:	Five years from the approval date listed above

The application was **APPROVED** subject to the following conditions:

Conditions of approval

- All serious adverse events must be reported via the Research Integrity and Ethics Team (ethics@liverpool.ac.uk) within 24 hours of their occurrence.
- If you wish to extend the duration of the study beyond the research ethics approval expiry date listed above, a new application should be submitted.

- If you wish to make an amendment to the research, please create and submit an
- amendment form using the research ethics system. If the named Principal Investigator or Supervisor leaves the employment of the University during the course of this approval, the approval will lapse. Therefore it will be necessary to create and submit an amendment form using the research ethics system.

- It is the responsibility of the Principal Investigator/Supervisor to inform all the investigators of the terms of the approval.

Kind regards,

D Prescott

Health and Life Sciences Research Ethics Committee (Human participants, tissues and databases) edreseth@liverpool.ac.uk

0151 795 4358

Appendix - Approved Documents

Page 1 of 2

(Relevant only to amendments involving changes to the study documentation)

The final document set reviewed and approved by the committee is listed below:

Document Type	File Name	Date	Version
Participant Consent Form	Participant consent form		
Study Proposal/Protocol	Protocol for DCE _FINAL	21/02/2018	1.3
Interview Schedule	Interview schedule_Parents	21/02/2018	1.0
Interview Schedule	Interview schedule_Healthcare providers	21/02/2018	1.0
Participant Consent Form	Participant consent form	27/02/2018	1.3

Questionnaire	DCE_Healthcare providers	27/02/2018	1.4
Questionnaire	DCE_Parents	27/02/2018	1.4
Participant Information Sheet	Participant information sheet_Questionnaire_Healthcare providers	07/03/2018	1.5
Participant Information Sheet	Participant information sheet_Questionnaire_Parents	07/03/2018	1.7
Participant Information Sheet	Participant information sheet_Focus group interview_Healthcare providers	07/03/2018	1.5
Participant Information Sheet	Participant information sheet_Focus group interview_Parents	07/03/2018	1.4

Appendix 2 – Poster to recruit for focus groups

PERFORM
Personalised Management of Febrile Illness

UNIVERSITY OF LIVERPOOL

Invitation to take part in research study

What matters to parents if your child is being treated for fever?

Fever is very common in children, and accounts for almost 20% of all emergency department visits. We are running a study to better diagnose causes of fever with new tests, but before we start using them we want to how these may affect parents. We want to better understand what parents would like when their child is being managed/investigated for potential causes of fever, and we would like to ask you your opinions.

We are planning a series of two 1 hour focus-groups:

- Thursday 5th July, 2018 10a.m-11a.m (Under 2s)
- Thursday 5th July, 2018 11.15a.m-12.30p.m (Under 1s)

We will provide consent forms on the day if you are happy to participate. We are just looking to hear your opinions and recommendations and boxes of chocolates will be provided as a thank you for taking part.

If you would like to take part in this research study please speak to Bernie Mossman for further details, or come along on the day.

Treating children with fever: What matters to parents? A focus-group

You are being invited to participate in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information, and watch the presentation that is provided carefully. Feel free to ask us if you would like more information, or if there is anything that you do not understand. Please also feel free to discuss this with your friends and relatives. We would like to stress that you do not have to accept this invitation and should only agree to take part if you want to.

Thank you for reading this.

1. What is the purpose of the study?

Many children who come to accident & emergency have a fever, there are many causes of fever and though some are a lot more serious than others, it is often difficult to tell them apart. Tests currently used can take a long time, are susceptible to contamination, and have a low sensitivity for identifying serious conditions. This means healthcare providers may often feel the need to provide antibiotics and additional tests while waiting, just to be on the safe side. New tests are now in development, and these may change how children with fever are assessed and treated.

The aim of this research is to find out:

- The most important things to healthcare providers when caring for a child with fever in the ED.
- Which things, e.g. waiting times, costs, pain, and the chance of getting antibiotics, are most important?

2. Why have you been chosen to take part?

You have been chosen to take part as you are involved in the delivery of care to children with febrile illness.

3. For what reasons should I not take part?

If you have difficulty listening, reading, and communicating in English.

4. Do you have to take part?

Participation is voluntary. You are free to withdraw at **ANY TIME**, and without explanation.

5. What will happen if you take part?

If you agree to take part, you will be asked to answer a series of questions about what you feel is important when caring for a child with fever. This will be done in the form of a focus group. You will be invited to discuss your opinions and those of others in the group and determine what matters to you when managing fever in accident and emergency.

You will also be asked some basic personal information questions (your age, your medical grade, years of experience, and whether you have personally witnessed instances of complications following severe bacterial infections, including sepsis, amputation, or death).

All information will remain confidential, and we will not contact you again after the study (unless you wish to provide your details to be informed of the results of this, and subsequent related studies). You have no responsibilities to the study once you have completed the focus group. The research is being carried out by a team at the University of Liverpool, and all responses during the focus group will be recorded (written and sound recording) by a single researcher (Simon Leigh). Your responses and recordings will be held securely by the University of Liverpool in a password protected computer folder. Once the research is completed, your responses (written and recorded) will be archived securely, again in a password protected folder, as per University protocol. If you do provide personal details to be contacted regarding study results, these too will be stored on a password protected University computer.

A short presentation will be provided if you agree to take part in the focus group which will explain the aims of the study, and participants will be free to ask any questions they may have at this point.

6. Expenses and/or payments

There are no payments for taking part in this research, however refreshments will be provided.

7. Are there any risks if I take part?

There are no risks associated with this research. You will not be contacted again, and no personal details will be taken (unless you wish to be informed of the results of this, and subsequent related studies). If you experience any discomfort at all when participating in this research, you should let the researcher know immediately and withdraw from the study.

8. What if I am unhappy or if there is a problem?

If you are unhappy, or if there is a problem, please feel free to let us know by contacting the PERFORM team, by email at PERFORM@liv.ac.uk, and we will try to help. If you remain unhappy or have a complaint which you feel you cannot come to us with then you should contact the Research Ethics and Integrity Office at ethics@liv.ac.uk. When contacting the Research Ethics and Integrity Office, please provide details of the name or description of the study (so that it can be identified), the researcher(s) involved, and the details of the complaint you wish to make.

9. Will my participation be kept confidential?

Yes. No personally identifiable data will be collected (unless you wish to be notified of the findings of this and subsequent related studies). If you do wish to be contacted, your data will be held securely by the University of Liverpool in a password protected computer folder. Once research is completed, responses and recordings will be archived securely as per University protocol.

10. What will happen to the results of the study?

The University of Liverpool aim to publish the results of this study in a medical journal. We will not contact you to inform you of the findings of this and subsequent related studies, unless

you inform the researcher that you wish to be notified of any findings, and are happy to provide contact details in order to do so. You will not be identifiable from the results of the study.

11. What will happen if I want to stop taking part?

You can withdraw from the study at any time, without explanation.

12. Who can I contact if I have further questions?

If you have any further questions you can contact:

The PERFORM team

Email: PERFORM@liv.ac.uk

Appendix 4 – Focus group : Consent form

Participant consent form

Version number: 1.0

Date: 16th January 2018

Title of the research project: Treating children with fever: What matters to parents?

Researcher(s): Prof. Enitan Carrol, Prof. Louis Niessen, Simon Leigh

Please initial box

1. I confirm that I have read and have understood the information sheet dated [16th January 2018] for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my rights being affected. In addition, should I not wish to answer any particular question or questions, I am free to decline. ☐
3. I understand that, under the Data Protection Act 1998, I can at any time, ask for access to the information I provide and I can also request the destruction of that information if I wish. ☐
4. I agree for the data I provide to be archived at the Institute of Infection and Global Health. I understand that other authorised researchers will have access to this data only if they agree to preserve the confidentiality of the information as requested in this form. ☐
5. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications ☐
6. I understand and agree that once I submit my data it will become anonymised and I will therefore no longer be able to withdraw my data. ☐
7. **I agree to take part in the above study.** ☐

_____	_____	_____
Participant name	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 5 – Syntax for DCE used for nGene

Design
;alts = Treatment A, Treatment B
;rows = 28
;eff = (mnl, d)
;block = 2

;model:
U(Treatment A) = b1[-0.01]* TimeinED[1,2,3,4] + b2.dummy[-0.01] * Pain[0,1] + b3[0] * Antibiotics[7,20,33] + b4.dummy[0] * Rapidtestattriage[0,1] + b5[-0.01] * Cost[7,12,20] + b6.dummy[0|0] * Provider[0,1,2] /
U(Treatment B) = b02[0] + b1[-0.01]* TimeinED[1,2,3,4] + b2.dummy * Pain[0,1] + b3[0] * Antibiotics[7,20,33] + b4[0] * Rapidtestattriage[0,1] + b5[-0.01]* Cost[7,12,20] + b6.dummy[0] * Provider[0,1,2]

Original research

OPEN ACCESS

What matters when managing childhood fever in the emergency department? A discrete-choice experiment comparing the preferences of parents and healthcare professionals in the UK

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ABSTRACT

Background Fever among children is a leading cause of emergency department (ED) attendance and a diagnostic conundrum; yet robust quantitative evidence regarding the preferences of parents and healthcare providers (HCPs) for managing fever is scarce.

Objective To determine parental and HCP preferences for the management of paediatric febrile illness in the ED.

Setting Ten children's centres and a children's ED in England from June 2018 to January 2019.

Participants 98 parents of children aged 0–11 years, and 99 HCPs took part.

Methods Nine focus-groups and coin-ranking exercises were conducted with parents, and a discrete-choice experiment (DCE) was conducted with both parents and HCPs, which asked respondents to choose their preferred option of several hypothetical management scenarios for paediatric febrile illness, with differing levels of visit time, out-of-pocket costs, antibiotic prescribing, HCP grade and pain/discomfort from investigations.

Results The mean focus-group size was 4.4 participants (range 3–7), with a mean duration of 27.4 min (range 18–46 min). Response rates to the DCE among parents and HCPs were 94.2% and 98.2%, respectively. Avoiding pain from diagnostics, receiving a faster diagnosis and minimising wait times were major concerns for both parents and HCPs, with parents willing-to-pay £16.89 for every 1 hour reduction in waiting times. Both groups preferred treatment by consultants and nurse practitioners to treatment by doctors in postgraduate training. Parents were willing to trade-off considerable increases in waiting times (24.1 min) to be seen by consultants and to avoid additional pain from diagnostics (45.6 min). Reducing antibiotic prescribing was important to HCPs but not parents.

Conclusions Both parents and HCPs care strongly about reducing visit time, avoiding pain from invasive investigations and receiving diagnostic insights faster when managing paediatric febrile illness. As such, overdue advances in diagnostic capabilities should improve child and carer experience and HCP satisfaction considerably in managing paediatric febrile illness.

What is already known on this topic?

- Children with fever account for 10%–20% of emergency department attendances, yet little is known about the preferences of healthcare providers (HCPs) and parents regarding management.
- Diagnosing a definitive cause of fever is often an iterative and protracted process, which may inconvenience both patients and parents, and require significant resources from HCPs.
- Efforts to reduce diagnostic uncertainty are focusing on the development of point-of-care testing; however, evidence regarding preferences, potential uptake and outcomes in emergency care is limited.

What this study adds?

- Avoiding pain from diagnostics and minimising time to diagnosis and discharge are major concerns for parents and HCPs when investigating paediatric febrile illness.
- Reducing antimicrobial prescribing is the single largest concern for HCPs. Conversely, parents exhibited no preference for/against antibiotics, contrary to existing evidence.
- Children, carers and HCPs are all likely to benefit considerably from upcoming advances in diagnostics, which are expected to provide increased confidence in timely decision making.

INTRODUCTION

Children with fever account for 14% of emergency department (ED) attendances in England.[1 2] Though most display signs and symptoms suggestive of specific infections; in ~20% of cases, there is no obvious cause.[3 4] These children are a concern to healthcare providers (HCPs), due to a small but significant risk of life-threatening bacterial infections,[5] which can have catastrophic consequences if undetected.

Diagnosing the source of fever is therefore a lengthy process, often including both blood and urine investigations, radiography and in some cases lumbar puncture.[6] Invasive investigations may inconvenience both patients and parents; and consequently, efforts to reduce diagnostic uncertainty are focusing on the development of protein-based or RNA signatures, delivered via point-of-care (POC)

testing. Evidence from primary care suggests that such tests may be effective in preventing clinically unnecessary antibiotic use and empiric investigations;[7–9] however, evidence in emergency care is lacking, and there is currently little agreement as to whom such tests should be used for.[10 11]

Decisions made during the management of paediatric febrile illness mitigate diagnostic uncertainty and contribute to patient and carer satisfaction with care. Parental anxiety and fear of serious but rare illness, including sepsis,[4] can result in parents of febrile children expecting antibiotics even when not clinically indicated,[12 13] while some may prefer their child to be managed by a more experienced clinician.[14 15] With the development of more sensitive, accurate and faster diagnostics, processes for investigating febrile illness are likely to change. What is unclear, are the expectations of parents and HCPs alike when managing paediatric febrile illness.

We conducted a series of focus-groups and a discrete-choice experiment (DCE) among parents and HCPs, to determine preferences for existing and future paediatric febrile illness care pathways, establishing the likely impact and success of implementing novel diagnostics for the management of paediatric febrile illness.

METHODS

We conducted focus-groups and discrete-choice surveys from June 2018 to January 2019 to determine parental and HCP preferences for the management of paediatric febrile illness. Participants consented in writing after being provided with a participant information sheet and having had the opportunity to ask questions. Demographic information for all respondents was collected immediately following consent.

Focus group discussions

We followed methodological guidelines from the International Society for Pharmacoeconomics and Outcomes Research,[16] identifying attributes of potential importance through a literature review, discussion with experts in paediatric infectious diseases, historical observational data[17] and focus-groups.

Initially, nine focus-groups took place with parents of children aged <11 years, in seven locations across the North-West of England between June and July 2018. The mean group size was 4.4 participants, with a mean duration of 27.4 min. Focus-groups were moderated by the principal researcher, and observed by staff from each venue, who were familiar with the participant groups. Respondents were invited to discuss any theme they considered relevant to the management of fever in children, with a focus on waiting times, preferred HCPs, staying overnight, having many tests, pain from investigations, antibiotics and time waiting to receive updates. Following the focus-groups, respondents were provided with printed labels and 100 coins, and asked to assign the coins to the attributes/labels they believed were most important. The results of this exercise can be found in online supplementary table 1. Following this exercise, the attributes 'staying overnight' and 'having lots of tests' were removed due to their respective lack of coins allocated. Although receiving antibiotics was the least important to parents, this was not ruled out due to the expected importance to decision making among HCPs. Finally, multicollinearity with 'time waiting in the ED', meant the theme 'time until receiving information/updates' was replaced with a binary variable of 'receive POC test' for the purpose of the DCE.

Discrete-choice experiment

DCE methodology is well described[18 19] and used extensively to measure patients' preferences for healthcare services. In DCEs, respondents are given a hypothetical scenario, typically comparing one option to another, and asked to choose which of the available options they prefer.[18 19] This process is repeated with the values (levels) of the characteristics (attributes) changing each time. The attributes used for our DCE are listed in table 1, with levels determined from responses obtained during the focus-groups and previously published data from our hospital.[17] The DCE was provided using paper forms and on a tablet-PC (the full survey is provided in online supplementary figure 1).

Table 1 Attributes and levels of the discrete-choice experiment

Attribute	Levels
Healthcare provider treating child	Doctor in postgraduate training* Nurse practitioner Consultant†
Pain experienced from investigations	Low Moderate
Likelihood of receiving antibiotics	Low (7%) Moderate (20%) High (33%)
Total time in the emergency department	1 hour 2 hours 3 hours 4 hours
Out-of-pocket cost to parent/guardian	£7 (~$9) £12 (~$16) £20 (~$26)
Receive rapid point of care test during triage	Yes No

*Consultant (UK) is equivalent to an attending physician in the USA.
†Foundation Year 1 and 2 in UK = Internship (North America and Europe).

There were two groups of respondents: (1) HCPs working in a children's ED and (2) parents recruited from children's soft play centres. We consecutively invited parents of children aged 0–11 years and excluded those unable to read/communicate proficiently in English. For HCPs, we included qualified nursing and medical staff of all grades with experience of managing febrile children, working within our tertiary care specialist hospital, located in the North West of England. Each respondent received 14 discrete-choice tasks plus two tests of rationality, one as the first task, to gauge understanding, and one as the final task, to measure sustained concentration. Failing either test of rationality led to responses being excluded from analysis. Respondents chose between two scenarios for managing paediatric febrile illness, characterised by differing levels of the attributes included (online supplementary figure 1). No opt-out option was included as this was deemed unrealistic in emergency care. As the full factorial experiment required ($3^3 \times 2^2 \times 4^1 = 432$) choices per respondent, a D-optimal design was chosen, with two blocks, with the order choice tasks were presented randomised using a random number generator. Surveys were pilot tested with 10 parents and 5 HCPs not involved in the main study to gauge interpretation and response times, during which period a researcher was available to answer any questions. Although sample-size calculations represent a technical challenge in DCEs, we used a parametric approach[20] to determine sample-size, equal to 48 respondents per group.

Data analysis

We used a mixed-logit model to estimate parental and HCP preferences for the management of paediatric febrile illness. Effects coding was used for all categorical variables; detailed

explanations of which are provided in online supplementary materials. To account for heterogeneity in preferences among our sample, including parents having different views on management by nurse practitioners, or doctors having different views on waiting times to nurses, it was assumed that population preferences for all effects-coded variables followed a normal distribution. As such, each individual preference observed constituted a random draw from this population distribution. Waiting times and costs were coded as linear continuous variables. We first estimated a main-effects model, and subsequently estimated subgroup effects, which for parents, were determined from the focus-group exercise, and included variables such as parent age, child age and the number of children a parent had. Due to a lack of qualitative research with HCPs prior to the DCE, subgroup analyses of HCP preferences were determined by the clinical lead for the study. Willingness-to-pay (WTP) and willingness-to-wait (WTW) analyses were performed to determine how respondents were willing to trade off attributes. CIs for WTP and WTW estimates were estimated via joint-distributed bootstrapping. All analyses were performed using Stata 14 (Stata) and deemed statistically significant at the 5% level.

RESULTS

Characteristics of participants

Between June 2018 and January 2019, 154 eligible parents and 101 eligible HCPs were identified. Fifty parents were invited to participate in focus-groups, 40 of whom accepted and 24 of which took part in the coin-ranking exercise. The remaining 104 parents and 101 HCPs were invited to take part in the DCE. Two parents and one HCP did not complete the DCE and four parents and one HCP declined to take part, leaving a total of 98 parents and 99 HCPs (online supplementary figure 2). No one failed either of the tests of rationality, resulting in a 100% understanding rate. Tables 2 and 3 illustrate the demographics of those completing the DCE in the parental and HCP cohorts, respectively.

Parental and HCP preferences for the management of febrile illness

In the DCE, 5/6 attributes for parents and 6/6 attributes for HCPs were statistically significant, suggesting importance with respect to the management of paediatric febrile illness. Table 4 illustrates preferences for each characteristic. Pain/discomfort associated with investigations, and total time in the ED were associated with significant dissatisfaction in both the parental and HCP groups. For HCPs, providing a POC test during triage, which may provide diagnostic information earlier, was associated with significantly increased satisfaction with care. Parents exhibited no preferences for receiving antibiotics, suggesting this is not a meaningful influencer of satisfaction with care in this group; however, for HCPs, a high likelihood of receiving antibiotics was associated with significant disutility. Finally, treatment by doctors in postgraduate training reduced satisfaction with care among both the HCP and parent groups.

Differences in parents' and HCP's preferences for the management of paediatric febrile illness

Reducing pain from investigations was important among all parent and HCP groups, as was receiving a rapid test during triage. Parents with >1 child and those aged >35 displayed significantly stronger preferences for minimising visit time and receiving consultant-led care, than those with fewer children and those aged <35, as demonstrated in figure 1A. Parents educated

Table 2 Characteristics of parents

	Percentage	Number
Characteristics of parents (n=98)		
Age (years)		
21–25	9.1	9
26–35	48.5	48
36–45	33.3	33
46–55	5.1	5
Prefer not to say	2.0	2
Gender		
Female	78.6	77
Male	21.4	21
Educational status		
High school	9.1	9
College	28.3	28
University	33.3	33
Masters	13.1	13
Professional	4.0	4
Doctorate	6.0	6
Other	1.0	1
Prefer not to say	3.0	3
Annual household income		
<£25 000	35.4	35
£25 001–£40 000	21.2	21
£40 001–£80 000	31.2	31
>£80 000	8.1	8
Prefer not to say	16.2	16
Where would you go first if your child had a fever?		
Pharmacy	14.1	14
Walk in centre	14.1	14
General practitioner	37.4	37
NHS 111*	25.2	25
Emergency department	2.0	2
None of the above	5.1	5
Characteristics of children		
Age of youngest child		
<1 year	38.3	38
1–3 years	34.4	34
4–6 years	12.1	12
7–10 years	12.1	12
11+ years	1.0	1
Age of oldest child		
<1 year	24.2%	24
1–3 years	23.3	23
4–6 years	21.2	21
7–10 years	15.2	15
11+ years	14.1	14
Number of children		
1	47.5	47
2	35.4	35
3	11.1	11
4	0.0	0
5+	2.0	2
Last time any of your children had a fever?		
<3 months	14.1	14
3–6 months	14.1	14
7–12 months	37.4	37
1–2 years	25.2	25
2+ years	2.0	2
None of the above	5.1	5

*NHS 111 is a telephone service for if you have an urgent medical problem and you are unsure what to do.
NHS, National Health Service.

Table 3 Characteristics of HCPs completing the DCE

Characteristics of healthcare professionals (n=99)	Percentage	Number
Age (years)		
21–25	8.1	8
26–35	57.6	57
36–45	20.2	20
46–55	11.1	11
56+	3	3
Prefer not to say	0.0	0
Years of experience as a HCP		
<5 years	41.4	41
6–10 years	28.3	28
11–15 years	14.1	14
16–20 years	7.1	7
21+ years	9.1	9
Experience working with children		
<5 years	43.4	43
6–10 years	25.3	25
11–15 years	14.1	14
16–20 years	8.1	8
21+ years	9.1	9
Clinical grade		
Healthcare assistant	10.1	10
Staff nurse	28.3	28
Senior staff nurse/Sister	19.2	19
ST1/2	12.1	12
ST3/4	23.2	23
Advanced nurse practitioner	4	4
Consultant	3	3

DCE, discrete-choice experiment; HCP, healthcare provider.

to college level or less were less concerned about being managed by a doctor in postgraduate training than those having completed higher education. A moderate/high probability of receiving antibiotics reduced satisfaction among those educated to University level or higher, or with a household income of >£40 000 per year, yet among those educated to college level or less, or with a household income of <£40 000 per year, receiving antibiotics did not affect utility, as shown in figure 1B. All HCP subgroups preferred not to prescribe antibiotics, but none more so than doctors, who also exhibited a stronger preference for rapid-testing than nurses (figure 1C).

Trade-offs: willingness-to-pay and willingness-to-wait

Parents were willing-to-pay £16.89 (95% CI £8.30 to £26.88) for a 1 hour reduction in total visit time, and £12.83 (95% CI £8.61 to £17.05) to avoid pain from diagnostic investigations. Parents were also WTP £6.77 (95% CI (–) £0.37 to £10.71) to see a consultant, if the alternative was management by a doctor in postgraduate training. Parents expressed a WTW an additional 45.6 min (95% CI (–)19.3 min to 60.4 min) to avoid pain from investigations and 24.1 min (95% CI (–)15.9 min to 46.9 min) for management by a consultant. HCPs were willing to extend waiting times by 39.9 min (95% CI (–)30.9 min to 79.5 min), provided it reduced the likelihood of prescribing antibiotics.

DISCUSSION

In this first-of-its-kind study, we found that parents and HCPs agree regarding what matters during the management of paediatric febrile illness, a finding which provides reassurance when considering the future implementation and acceptability of novel diagnostics within EDs. Both groups were most concerned about reducing ED visit time, receiving diagnostic information faster and avoiding pain from investigations. The strength of this preference was similar across subgroups of differing sociodemographic characteristics. Parents also displayed strong preferences for being treated by consultants, rather than doctors in postgraduate training. Finally, the likelihood of receiving antibiotics did not significantly influence satisfaction among parents, whereas for HCPs, this was a significant concern. Because the availability of diagnostics is increasing, with CRP-POC testing now used in some UK primary care settings,[21 22] the findings of this study may be used to prioritise the implementation of upcoming diagnostics, to best meet the preferences of families and HCPs.

A systematic review of emergency medicine highlighted the most frequently identified that interpersonal skills/staff attitudes;

Table 4 Preferences in the management of paediatric febrile illness of parents and HCP

	Parents (n=98)		HCPs (n=99)	
	Coefficient	95% CI	Coefficient	95% CI
Staff grade				
Trainee doctor	–0.244*	–0.472 to –0.016	–0.204*	–0.398 to –0.099
Nurse practitioner	–0.135	–0.368 to 0.098	0.081*	–0.106 to 0.27
Consultant (reference group)	0.379		0.032	
Likelihood of receiving antibiotics				
Low (reference group)	0.143		0.729	
Medium	0.031	–0.865 to 0.803	–0.111	–0.594 to 0.371
High	–0.174	–0.74 to 0.392	–0.618*	–1 to –0.236
Moderate pain from investigations (relative to low)	–0.462*	–0.613 to –0.312	–0.439*	–0.558 to –0.32
Receive POC test during triage (relative to no)	0.627*	0.484 to 0.769	0.723*	0.562 to 0.884
Total time spent in the ED (per hour)	–0.608*	–0.78 to –0.435	–0.679*	–0.81 to –0.548
Out-of-pocket cost to parents (per £1)	–0.036*	–0.065 to –0.007	–0.051*	–0.074 to –0.028
Observations	2772		2774	
Log likelihood	–722.1		–674.8	

*Significant at 5% level. Table represents β coefficients and CIs from mixed logit regression. The regression coefficients for each attribute level represents the mean part-worth utility of that attribute level in the respondent sample. A positive value denotes utility/satisfaction, with a negative value denoting disutility/dissatisfaction.
ED, emergency department; HCP, healthcare provider; POC, point-of-care.

may direct low-acuity children to lesser experienced staff, as confidence in diagnostic processes increases, and with this, the seeking of second opinions from more experienced members of staff decreasing.

We identified a strong aversion to children experiencing pain from investigations. While observational data suggest the likelihood of venepuncture during the management of paediatric febrile illness is low,[17] pain from procedures including venepuncture is often the most traumatic experience when a child's primary symptom is fever, impacting patient experience significantly.[23 24] Additionally, studies demonstrate that parents tend to overestimate pain experienced by their children,[25–27] and therefore our findings suggest that while pain from venepuncture may be expected to last a few minutes, pain from obtaining a single drop of blood from a finger prick for POC testing may be more favourable, thereby improving the experiences for both parents and children.

While substantial literature regarding the management of febrile illness suggests antibiotics are commonly sought by parents,[28–31] we did not observe this. HCPs demonstrated a strong preference for avoiding antibiotic use where possible, likely a result of increased awareness of the growing threat of antimicrobial resistance; however, parents were indifferent to antibiotic use. This may be explained in part by increased efforts to educate the general population, with television programmes such as 'Trust me I'm a doctor', and Public Health England's 'keep antibiotics working' jingle[32] being just two examples. As such, any novel diagnostics which provide diagnostic information within the window in which precautionary antibiotics are usually considered, are likely to improve HCP satisfaction and patient outcomes, resulting from reduced antimicrobial resistance.

The strengths of our study include the in-depth process for determining attributes of importance, the variety of subgroup analyses performed, and that this study is a first-of-its-kind in measuring preferences for the management of paediatric febrile illness. The findings of this study should, however, also be viewed in the context of several limitations. First, our parent population were sought from the community including playgroups, sure-start centres and parent-teacher associations, rather than those presenting to the ED with fever. While this may be considered a strength in the context of government funded healthcare systems, as the public effectively pays for the National Health Service, this may have affected the accuracy of our results due to recall bias. Second, the sample sizes in the parental and HCP DCEs were limited, which makes robust, precise conclusions, particularly among subgroups, difficult, while the generalisability of our findings may also be limited by all respondents residing in the UK. It is possible that preferences for the attributes considered may differ in other healthcare settings; this was not accounted for in our analysis. Finally, while every effort was made to ensure that the attributes chosen were important to parents and HCPs alike, we could not include every important variable, and as such, it is possible that factors which are influential in determining satisfaction with care were omitted, an issue which future research should aim to address.

CONCLUSION

This is the first DCE conducted with parents and HCPs on the choice processes of managing febrile children in the ED. Parents and HCPs feel strongly about reduction of visit time, avoidance of pain and faster diagnosis in the context of managing paediatric febrile illness but are willing to trade these off against each other. Overdue advances in diagnostic capabilities should improve child and carer experience and HCP satisfaction considerably, thus facilitating widespread acceptance and adoption of these technologies.

Contributors LN and EDC designed and formulated the research question. SL, JR, SY and FC assisted in study design. SL conducted all interviews and surveys, organised the data and conducted analyses. SL, EDC, LN and JR wrote the first draft of the paper. All authors contributed to the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study received ethical approval from the Health and Life Sciences Research Committee at the University of Liverpool, reference number 3032.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Chapter 4 – Publication contribution statement

LN and EDC designed and formulated the research question. SL, JR, SY and FC assisted in study design. SL conducted all interviews and surveys, organised the data, performed the pilot study and conducted all statistical analyses. SL, wrote the first draft of the paper. All authors contributed to the final manuscript.

Chapter 5: Management of non-urgent paediatric ED attendances by general practitioners: Impact on clinical, operational, and economic outcomes from a large retrospective observational study

Abstract

Background ED attendances with non-urgent conditions are common, particularly among children. In such cases primary care management may not only be more clinically appropriate, but also improve patient experience and cost-effectiveness.

Aim To determine the impact of integrating a GP into a paediatric ED, on admissions, waiting times, antibiotic prescribing and treatment costs.

Design & Setting Retrospective cohort study of non-urgent ED presentations in a large paediatric tertiary hospital in North West England.

Method From October-2015 to September-2017, a GP was co-located within the ED seven days a week. Children triaged green using the MTS (non-urgent) were considered 'GP appropriate'. We compared healthcare costs and clinical outcomes of non-urgent children managed by a GP, with those managed by ED-staff over the same period.

Results 13,099 children were designated as 'GP appropriate', 8,404 (64.2%) were managed by GPs and 4,695 (35.8%) by ED staff. Median duration of ED stay was

39min (IQR 16-108) in the GP-group and 165min (IQR 104-222) in the ED-group ($p<0.001$). The GP-group were less likely to: be admitted as inpatients (OR 0.16, 95% CI 0.13 - 0.2) and wait longer than four-hours (OR 0.1, 95% CI 0.08 - 0.13), but more likely to receive antibiotics (OR 1.42, 95% CI 1.27 - 1.58). Additionally, treatment costs were 18.4% lower in the GP-group (£115 vs. £141 per-patient), $p<0.0001$.

Conclusion Integrating GPs into paediatric EDs is likely to reduce waiting times, inpatient admissions and healthcare costs significantly, but also increase antibiotic prescribing. In the current context of rising demand for children's emergency services, this study provides insights to support the ongoing development of 'GP in ED' models of care.

Background

The previous chapters of this thesis have demonstrated that the economic, parental and societal costs of diagnostic uncertainty when managing paediatric febrile illness in the ED are considerable (Leigh, Mehta, et al. 2020) (Leigh, Grant, et al. 2018). As a result, the subsequent value of diagnostic innovation is also likely to be high. This suggests a clear operational and economic benefit from any diagnostic modality which can better identify the needle among the febrile haystack, find the small number of children who require more intensive investigation, and prevent the overtreatment of the majority of children who will most likely be suffering from self-limiting viral infections (Barbi, et al. 2017) (Manzano, et al. 2011). This is particularly important when considering the current demand for ED services. It is estimated that the total number of visits to EDs in England exceeded 24 million in 2018 (Kmietowicz 2018),

a rise of 42% over the last 12 years (Steventon, et al. 2018), with two-thirds (HSCIC 2016) of attendances taking place without GP referral or transfer by ambulance. A significant proportion of these attendances can be attributed to febrile children, with ED admission rates for upper respiratory tract infections increasing by 22%, lower respiratory tract infections by 40%, UTIs by 43% and gastroenteritis by 31%, over a similar period (Gill, Goldacre, et al. 2013).

Even though many ED attendances may result from an acute medical problem, they may not always require immediate specialized emergency medical care. It is estimated that between 15% (Smith, et al. 2018) and 79% (Gnani, et al. 2016) of ED visits by children are classified as non-urgent. While these data are broad and representative of all reasons resulting in ED attendance, high volumes of non-urgent attendances are well documented with regard to paediatric febrile illness (Piller and Herzog 2019) (Morrison, et al. 2014), and which from data generated as part of this thesis (defined as triaged MTS Green or less), occur more than 50% of the time (Leigh, Grant, et al. 2018).

Confidence in the quality and investigative ability of ED care (Butun, Linden and Lynn 2019) difficulty in obtaining (Steele, Coote and Klaber 2019), or confidence in primary care appointments (O'Cathain, et al. 2020), are likely to play a significant role in this process, as too is parental concern regarding the potential severity of conditions (Penson, Coleman and Mason 2012), anxiety, and a perceived need for urgent treatment (Butun, Linden and Lynn 2019) (Smith and Roth 2008) (Truman and Reutter 2002) (Williams, O'Rourke and Keogh 2009). Each of these factors have been shown to exacerbate the problem of non-urgent attendances in children's emergency

medicine, both in previously published literature, and from a preference perspective, within the previous chapter of this thesis (Leigh, Robinson, et al. 2020).

Additionally, many children who attend the ED are admitted for short-stay admissions. Once admitted, children are at risk of hospital-acquired infections, medical errors (Gill, Goldacre, et al. 2013), drug reactions and emotional trauma (Flores 2005). The previous chapter highlighted that parents and HCPs clearly prefer the management of febrile children to be less invasive. This is characterised by less pain and discomfort from diagnostics where possible, and for care processes to be more streamlined; for waiting times to be reduced, and therefore the opportunity for anxiety while waiting in the ED, to be minimised. Given that an increasing number of non-urgent ED attendances are amenable to treatment in primary care, one of the key recommendations of the Royal College of Emergency Medicine is to co-locate primary care services within ED settings (RCEM 2014). The benefits of introducing GPs in EDs for managing non-urgent cases, while in their infancy, provide some preliminary suggestions of benefit. These include increased patient satisfaction (Kmietowicz 2014) (Smith, et al. 2018), reduced waiting times (Goodman, Gordon and Martin 2014) (Smith, et al. 2018), and reductions in invasive examinations (Khangura, Flodgren and Perera 2012).

As a result, the implementation of GP-led emergency care pathways for the management of non-urgent presentations (not limited to paediatric febrile illness); may result in improvements not only in patient satisfaction, but also economic outcomes.

Building on previous findings from a 6-month pilot scheme of this initiative (Smith, et al. 2018), assessing clinical and process outcomes only, this study assesses the impact of ED co-location of a primary care service on waiting times, admissions, antibiotic prescribing rates and healthcare costs; to determine the cost-effectiveness of ED co-location of GP services, for non-urgent presentations. The findings of this chapter were published in January 2021 in the British Journal of General Practice (Leigh, Mehta, et al. 2020).

Materials & Methods

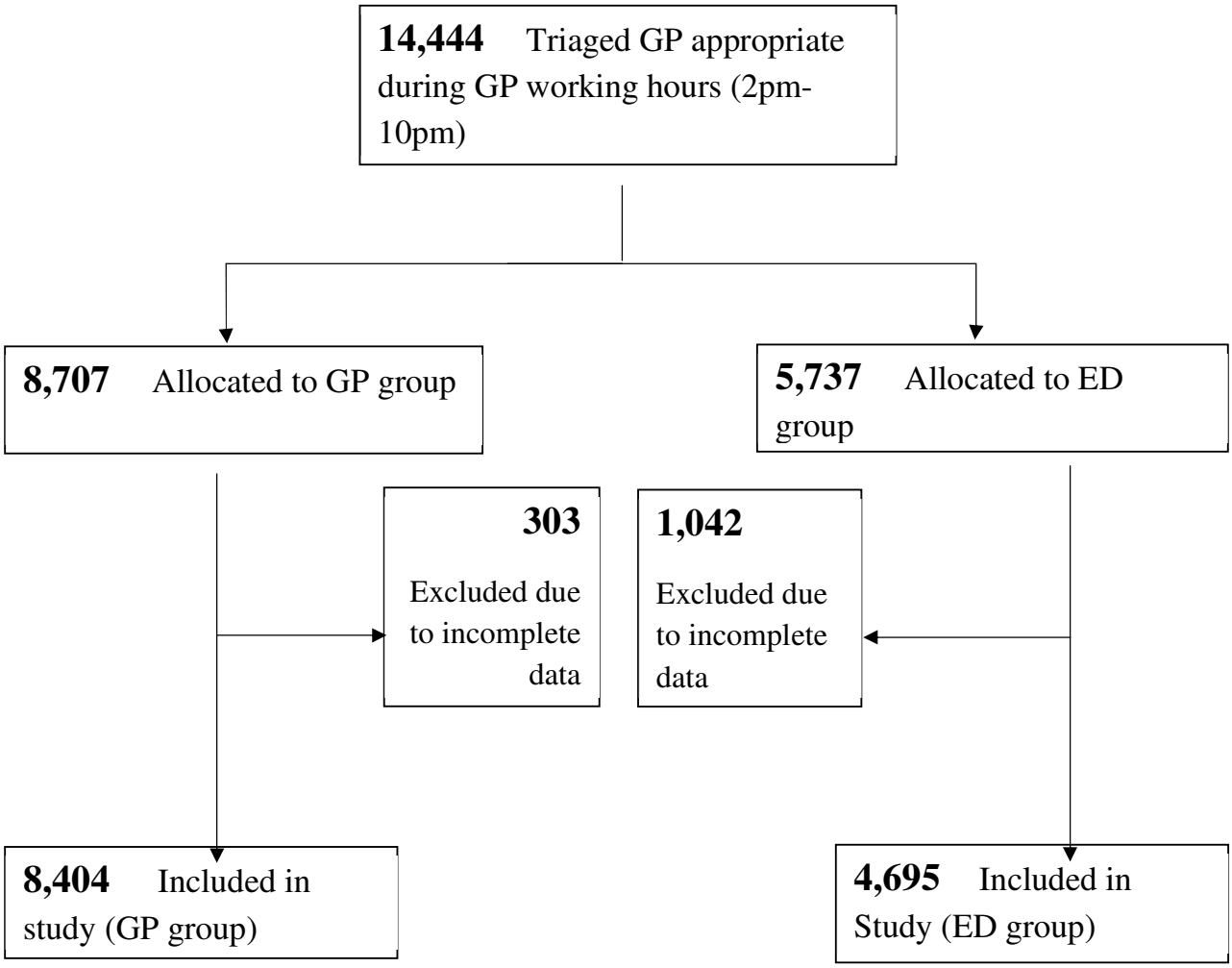
Study setting, population, and design

The study was conducted retrospectively in the ED of a large paediatric hospital located in the Northwest of England. From 1st October 2015 to 31st September 2017, GPs employed by a Liverpool-based social enterprise delivering NHS services (Primary Care 24, formerly Urgent Care 24), were available in the ED as a separate but co-located service. The service ran from 14:00-22:00h, seven-days-a-week.

All children were initially evaluated by a qualified ED nurse using the MTS (Zachariasse, et al. 2017). Low-acuity children triaged as non-urgent (MTS Green in the absence of comorbidities), were labelled "GP appropriate" and allocated to be seen by the GP during its operational hours. Parents were not given a choice of allocation to the GP or otherwise but were informed, at which point they could refuse the service. Children referred to the ED by their own GP or a walk-in centre were ineligible for allocation to the GP in the ED service.

In instances of GP non-availability, children triaged as GP appropriate who would otherwise have been managed by onsite GPs, were instead managed by ED clinical staff, following the standard procedures of the service (the comparator group). This intervention presented an opportunity to evaluate a "natural experiment" comparing both outcomes (antimicrobial prescribing, waiting times, admission rates and achievement of the Department of Health and Social Care four-hour target), and costs of children presenting to our paediatric ED with the same clinical urgency (MTS Green), over the same time period (2pm-10pm, 7-days a week). Differing only in terms of who provided treatment, ED teams or the co-located GP service. Details of study recruitment are provided in Figure 27.

Figure 27: Flow diagram of study recruitment



Due to the retrospective observational nature of the study, in addition to primary outcome data, data concerning potential confounders were collected for all patients, from both ED and GP services databases. For all cases, information on arrival and discharge date and time, final diagnosis, discharge status, antimicrobial prescribing,

and attending physician were available. Demographic (age, gender, home postcode, Index of Multiple Deprivation-2015 (IMD) score) and clinical data (oxygen saturation, temperature, and pulse) were also collected. For patients presenting with fever who received antibiotics, an assessment of whether antibiotic prescribing was clinically necessary was made. Diagnostic categories, defined as definite bacterial, probable bacterial or bacterial syndrome with low/no inflammatory markers (collectively bacterial aetiology), definite viral, probable viral, or viral syndrome with no/high inflammatory markers (collectively viral aetiology), trivial illness, inflammatory illness, and unknown/insufficient information, were applied retrospectively, based on an adapted algorithm from Herberg et al (Herberg, et al. 2016). In any instance where uncertainty or disagreement occurred regarding the appropriate classification, these cases were marked and decided upon by two consultants specializing in paediatric infectious diseases. All cases had notes, including CRP, neutrophils and sterile site pathogenic bacteria recorded such that diagnosis classifications could be quality checked to ensure consistency. All sub-group analyses were additionally applied to the cohort of children presenting with fever.

Statistical analysis

Patients triaged as "GP appropriate" and managed by the GP service (exposed group) were compared with patients triaged as "GP appropriate" and managed by ED staff over the same time period (control group), using an intention-to-treat approach. Descriptive statistics were generated for both groups. Differences in proportions were analysed using the Chi-square test, with differences in continuous outcomes assessed

via using the Mann-Whitney U-test. Multivariate logistic regression was used to estimate odds ratios for binary outcomes, including hospital admission, antimicrobial prescribing and the likelihood of leaving before being treated. Each multivariate logistic regression analysis was adjusted for potential imbalances in baseline covariates which may have impacted outcomes. These included whether children were re-attending the ED within a five-day period, an indicator of prolonged and un-improving illness, or whether they had previously sought care from their GP. Sub-group analyses were additionally performed to account for the impact of covariates previously shown to impact the outcomes under consideration, including patient age (Leigh, Grant, et al. 2018) (Berry, et al. 2008), working diagnosis (Leigh, Grant, et al. 2018), and deprivation (Wise 2015). All statistical analyses were conducted using STATA 12 (Stata Corporation, College Station, TX, USA), with statistical significance defined at the usual 5% level.

Costing and resource-use analysis

Healthcare resource use was calculated using a TDABC approach, as used within previous health economic analyses conducted in the ED (Leigh, Grant, et al. 2018), including Chapter 3 of this thesis. TDABC identifies all instances and durations of interaction with health service personnel during a treatment episode and assigns time-dependent costs to each (triage, consultation, cannulation etc), based on stopwatch timing combined with the hourly salaries of the staff involved. These timing estimates and unit costs used for the patient-level healthcare costing are provided in Tables 22 and 23. Finally, adding unit costs of consumables including medicines, and tariff-

based items including investigations, radiography and inpatient admission spells provides an estimation of total resource use during a treatment episode. Further details of the methodology for the costing exercise are provided elsewhere (Leigh, Grant, et al. 2018). Societal costs to parents of waiting in the ED were also estimated, by cross-referencing each respondent's postcode with hourly income data matched per lower layer super output area, which was obtained from the Office for National Statistics (ONS 2018). While not necessary from an NHS perspective, this enabled a much deeper understanding of the wider impact of the two management protocols for non-urgent ED presentations, enabling an estimation of the impact to parents.

Table 22: Staff time associated with components of the paediatric febrile illness pathway

ACTIVITY	MEAN DURATION (MINS)
Triage time (Nurse)*	4.5
Clinician consultation time (MTS Green) *	16.2
Clinician consultation time (MTS Yellow) *	19.4
Clinician consultation time (MTS Orange) *	21.1
Clinician consultation time (MTS Red) *	22.7
Clinician time - Writing up patient notes#	10
Order blood/urine culture (Clinician)#	10
Arrange X-ray (Clinician)#	6
Book patient into the ED (Receptionist)#	2
Refer patient to other specialties (Clinician)#	20
Insert cannula (Clinician)*	20
Provide antibiotics/other medicines (Nurse)#	5
Visual assessment triage (Nurse)*	2
Interpret results of ancillary investigations (Clinician)#	10
**Collected during time-in-motion study* *# Estimate provided by ED consultants*	

Table 23: Unit costs by component of paediatric febrile illness pathway

ITEM	UNIT COST
INVESTIGATIONS (PER TEST)	
Amylase	£6.00
Bacterial PCR	£158.00
Bilirubin	£6.00
Biochemistry Profile	£8.00
Blood albumin	£6.00
Blood glucose test	£6.00
Blood Culture	£35.00
Blood gas #	£7.00
Blood taken	£3.00
Calcium profile	£7.00
Clotting screen	£5.00
Creatinine	£6.00
CRP	£6.00
CSF	£6.00
CT scan (Head)	£201.00
ECG	£33.00
ENT Swab	£19.00
ESR	£4.00
FBC	£3.00
Glandular fever screen	£4.00
Group and save	£12.00
LFTs	£7.00
Magnesium	£6.00
Malarial parasites test	£21.00

Measles PCR	£55.00
Meningococcal/ pneumococcal PCR	£25.00
Meningococci screen	£6.00
Mycoplasma SER	£23.00
Pertussis swab	£9.00
Phosphate	£6.00
Rapid Strep Test	£9.00
Renal profile	£46.00
Respiratory PCR	£117.00
RSV screen	£12.00
Ultrasound	£55.00
Urinalysis #	£8.00
Urine albumin	£6.00
Urine culture	£8.00
Urine dipstick	£6.00
Urine Sample	£8.53
Virus PCR	£56.00
X-ray	£46.00
ANTIBIOTICS (PER DOSE/COURSE)	
Amoxicillin 125mg (Suspended) *	£1.16
Amoxicillin 125mg (IV) *	£4.34
Amoxicillin 250mg (Susp.) *	£1.33
Cefotaxime 195mg (IV) *	£0.48
Cefotaxime 575mg (IV) *	£0.66

NURSE TIME (PER HOUR)	
Band 5	£15.43
Band 6	£18.95
Band 7	£22.50
Band 8a	£27.39
DOCTOR TIME (PER HOUR)	
FY1/FY2	£24.24
ST1-3	£30.79
APNP	£27.39
Registrar	£39.02
Consultant	£76.11
GP	£116
INPATIENT ADMISSION	
Short stay (HRG PW20C, 3 days non-elective stay) #	£1,712
Excess bed day charge #	£462

Unit costs provided by hospital finance team unless otherwise stated:

 # NHS Reference costs 2018

** British National Formulary 2018*

All unit costs were in 2019 prices, with non-parametric bootstrapping (percentile method) used to generate 95% confidence intervals. Discounting of costs and outcomes was not required due to the short timeframe for analysis. Probabilistic sensitivity analysis was also performed to test for robustness of conclusions regarding the impact of GP-led care on healthcare costs and outcomes. The distributions employed to explore parametric uncertainty are provided in Table 24. All distributions

were fitted based on actual data obtained during this chapter and the previous chapters of this thesis.

Table 24: Distributions used for probabilistic sensitivity analysis.

PARAMETER	DISTRIBUTION
TIME (HOURS)	
Nurse triage	Gamma (4.69, 0.01)
Proportion performed by band 6 nurses	Beta (16,55)
Proportion performed by band 5 nurses	1- Beta (16,55)
Clinical consultation	Gamma (3.9, 0.04)
Clinician writing up patient notes	Uniform (1,20)
Arrange blood/urine culture	Uniform (1,25)
Arranging X-ray	Uniform (1,30)
Receptionist booking patient in	Uniform (1,5)
Clinician arranging referral	Uniform (1,25)
Clinician cannulating child	Uniform (5,35)
Nurse providing antibiotics to child	Uniform (1,10)
Visual assessment by nurse	Uniform (0.5,5)
Days spent as inpatient (if admitted)	Gamma (3.72, 1.03)
SALARY (COST/HOUR)	
Nurse (band 5)	Uniform (13.36,17.5)
Nurse (band 6)	Uniform (16.14,21.77)
Nurse (band 7)	Uniform (19.34,25.67)
Nurse (band 8a)	Uniform (24.8,29.99)
Foundation year doctor	Uniform (22.5,26)
ST1-3	Uniform (27, 30.8)
APNP	Uniform (24.8,29.99)
Registrar	Uniform (36,41)

Consultant	Uniform (64.8,87.4)

Results

Baseline characteristics & recruitment

Between October 1st, 2015 and September 30th, 2017, 14,444 children were triaged GP appropriate between 14:00 and 22:00 hours when the on-site GPs were in operation. Of these children, 1,345 had incomplete or missing data, resulting in a complete dataset of 13,099 observations. Table 25 shows the personal characteristics of both groups, with no significant differences observed in any demographic or clinical baseline characteristics.

Table 25: Characteristics of patients triaged as 'GP appropriate', attending the ED

Variable	GP group (n=8,404)	ED group (n=4,695)	Total (n=13,099)	Significance
Gender				p=0.206*
Male	4,268 (50.8%)	2,541 (54.1%)	6,809 (52%)	
Female	4,136 (49.2%)	2,154 (45.9%)	6,290 (48%)	
Age Category				p=0.785*
<3 months	613 (7.3%)	319 (6.8%)	932 (7.1%)	
3-6 months	538 (6.4%)	291 (6.2%)	829 (6.3%)	
6-12 months	1,277 (15.2%)	714 (15.2%)	1,991 (15.2%)	
1-3 years	3,177 (37.8%)	1,779 (37.9%)	4,956 (37.8%)	
4-10 years	2,017 (24%)	1,174 (35%)	3,191 (24.5%)	
11+ years	782 (9.3%)	418 (8.9%)	1,200 (9.1%)	
Age (years)				p=0.624#
Median (IQR)	2.2 (0.9-5.5)	2.15 (0.87-5.5)	2.17 (0.88-5.5)	
Deprivation quintiles				p=0.656*
1 (least deprived)	208 (2.7%)	106 (2.4%)	314 (2.6%)	
2	456 (5.9%)	253 (5.7%)	709 (5.8%)	

3	833 (10.7%)	504 (11.4%)	1,337 (10.9%)	
4	898 (11.6%)	528 (11.9%)	1,426 (11.7%)	
5 (most deprived)	5,378 (69.2%)	3,058 (68.7%)	8,436 (69%)	
Diagnosis				N/A
Respiratory Conditions	2070 (24.6%)	1076 (22.9%)	3,146 (24%)	
Gastrointestinal Conditions	1410 (16.8%)	695 (14.8%)	2,105 (16.1%)	
Infectious Disease	1194 (14.2%)	695 (14.8%)	1,889 (14.4%)	
Diagnosis Not Classifiable	530 (6.3%)	946 (20.1%)	1,476 (11.3%)	
ENT Conditions	679 (8.1%)	227 (4.8%)	906 (6.9%)	
Local Infection	561 (6.7%)	305 (6.5%)	866 (6.6%)	
Dermatological Conditions	302 (3.6%)	99 (2.1%)	401 (3.1%)	
Urological Conditions (Including Cystitis)	256 (3%)	128 (2.7%)	384 (2.9%)	
Allergy (Including Anaphylaxis)	263 (3.1%)	100 (2.1%)	363 (2.8%)	
Head Injury	190 (2.3%)	45 (1%)	235 (1.8%)	
Fever	1,289 (15.3%)	643 (13.7%)	1,932 (14.7%)	
Pulse (Beats per minute)				p=0.864#
Median (IQR)	127 (109-143)	125 (109-140)	126 (109-142)	
Temperature				p=0.767#
Median (IQR)	37 (36.6-37.6)	37 (36.6-37.6)	37 (36.6-37.6)	
Oxygen saturation (O_2 Sats)				p=0.558#
Median (IQR)	99 (97-100)	99 (97-100)	99 (97-100)	
Attended emergency department in last 5 days?				p=0.14*
Yes	160 (1.9%)	103 (2.2%)	263 (2%)	
No	8,244 (98.1%)	4,592 (97.8%)	12,836 (98%)	
Attended emergency department on a weekday?				p=0.84*
Yes	5,824 (69.3%)	3,301 (70.3%)	9,125 (69.7%)	
No	2,580 (30.7%)	1,394 (29.7%)	3,974 (30.3%)	
Attended emergency department during holiday period? **				p=0.134*
Yes	2,958 (35.2%)	1,592 (33.9%)	4,550 (34.7%)	
No	5,446 (64.8%)	3,103 (66.1%)	8,450 (65.3%)	

** χ (Chi-squared)*
 # Mann-Whitney U test
*** Holidays followed the English academic year and included half-terms, Easter, Christmas, and winter holidays.*

Prescription of antibiotics

Rates of antibiotic prescribing were 15.1% in the GP group and 10.8% in the ED group, $p<0.001$, (OR 1.42; 95% CI 1.27 to 1.58; $p<0.001$). Compared to children managed by ED teams, children managed by the GP who were seen and discharged within one-hour had an odds ratio of 3.32 (95% CI 2.2-5.0) for being prescribed antibiotics, compared to children seen and discharged within one hour by ED teams, as shown in Figure 28. Similarly, children managed by the GP group with fever at presentation experienced a 10.4% increase in antibiotic prescribing (27.1% vs. 16.7%). Approximately 89.9% of children with fever receiving antibiotics in the GP group, compared to 75.9% in the ED group, did not have a presumed or definitive bacterial aetiology (Table 26).

Figure 28: Odds-ratios for antibiotic prescribing by age and time until discharge

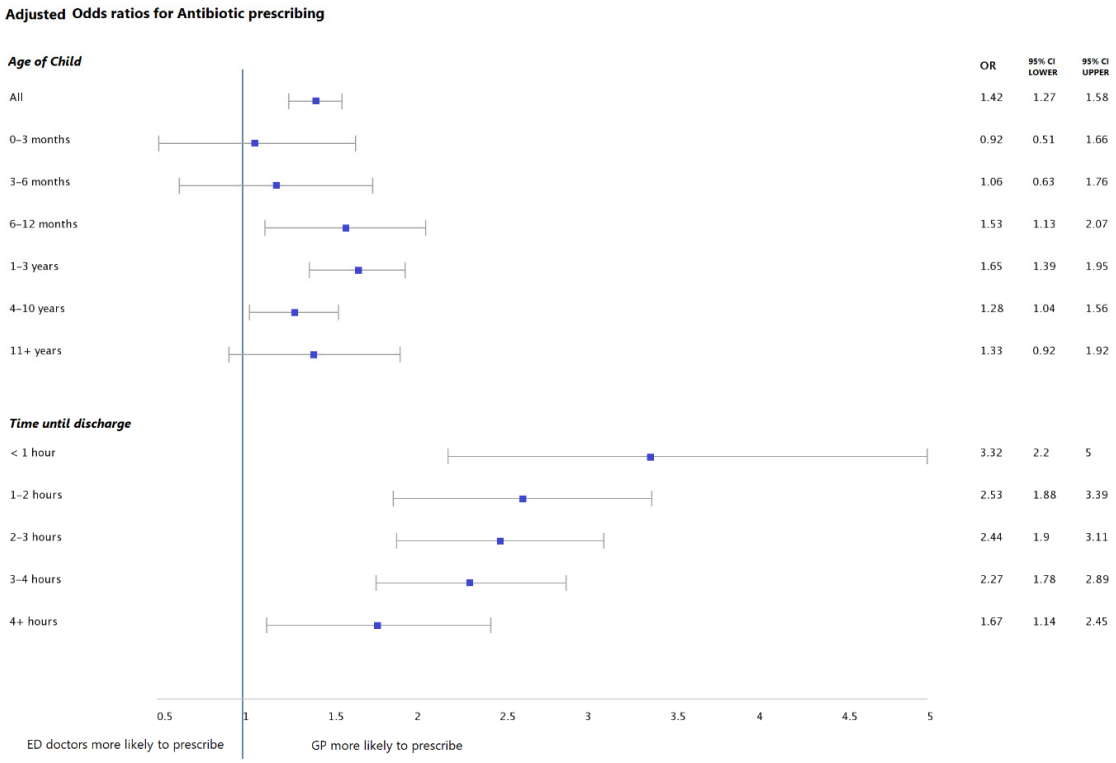


Table 26: Antibiotic use differentiated by aetiology of fever and treatment group

	GP Group (n=337)	**ED Group (n=112)**
Unknown bacterial or viral	290 (86.1%)	76 (67.9%)
Probable Viral	0 (0%)	3 (2.7%)
Definite Viral	0 (0%)	1 (0.9%)
Viral Syndrome	5 (1.5%)	3 (2.7%)
All Viral	5 (1.5%)	7 (6.3%)
Probable Bacterial	0 (0%)	2 (1.8%)
Definite Bacterial	7 (2.1%)	12 (10.7%)
Bacterial Syndrome	27 (8%)	13 (11.6%)
All Bacterial	34 (10.1%)	27 (24.1%)
Other infection	8 (2.4%)	2 (1.8%)
Trivial	0 (0%)	0 (0%)
Inflammation	0 (0%)	0 (0%)

Being seen within the UK Department of Health and Social Care 4-hour target

The median duration of stay in the ED was 39min (IQR 16–108) for the GP group compared with 165 min (IQR 104–222) for the ED group ($p<0.005$). Management by the onsite GP was associated with significantly reduced odds of breaching the Department of Health and Social Care four-hour waiting standard (OR 0.10; 95% CI 0.084 to 0.125; $p<0.001$), with 98.6% of children in the GP group and 88.4% in the ED group discharged or admitted within four hours. For children with fever as the presenting complaint, rates were similar with 98.5% of children in the GP group and 87.5% in the ED group discharged or admitted within four hours ($p<0.001$).

Admission to hospital

The odds of being admitted were significantly lower (84%) for children managed by the GP (OR 0.16; 95% CI 0.13 to 0.20; $p<0.001$). Short stay admissions of <6 hours were reduced by 84.7%, 6-24-hour admissions by 86.5% and admissions exceeding one day by 78.7% for those seen by the GP. For children with fever as the presenting complaint (n=1,926), the probability of inpatient admission increased four-fold ($p<0.001$). Children of all ages and diagnoses were statistically significantly more likely to be admitted to hospital if managed by ED clinical teams (all $p<0.001$). The grade of the ED clinician managing the child had no impact on admission rates.

Discharge status

In total, 95.9% of children in the GP group were discharged with no further action, or advised to seek follow-up with their own GP, compared to 76% in the ED group. Outpatient referrals were equivalent across groups with 107 (1.3%) of the GP group and 103 (2.2%) of the ED group referred. However, 9.7% of those in the ED group left before being seen, compared to 1.2% in the GP group, as demonstrated in Table 27.

Table 27: Discharge status of children by treatment group

Discharge	**GP group**	**ED group**	**Total**
Own GP follow-up	2,312 (27.5%)	287 (6.1%)	2,599 (19.8%)
Discharged	5,745 (68.4%)	3,282 (69.9%)	9,127 (69.7%)
Admitted	117 (1.4%)	374 (8%)	491 (3.7%)
Outpatient	107 (1.3%)	103 (2.2%)	210 (1.6%)
ED clinic	3 (<0.1%)	59 (1.3%)	62 (0.5%)
Community follow-up	1 (<0.1%)	0 (0%)	1 (<0.1%)
Left before seen	100 (1.2%)	455 (9.7%)	555 (4.2%)
Left following advice	1 (<0.1%)	5 (0.1%)	6 (<0.1%)
Left refusing treatment	6 (<0.1%)	117 (2.5%)	123 (1%)
Other	5 (<0.1%)	13 (0.3%)	18 (0.1%)

Healthcare and societal costs of ED management

The mean cost of treatment episodes for the GP group was £115.24 (95% CI £20.50-£351.67), compared to £141.16 (95% CI £11.78-£539.94) among those managed by ED clinicians, $p<0.001$. Both groups recorded similar costs attributable to medications, prescribing, and investigations (Table 28). Costs associated with staff salaries (receptionist, nurse, doctor) were much higher in the GP group, while inpatient admission costs were significantly lower, $p<0.001$, owing primarily to a 75.3%

reduction in median inpatient duration (0.22 days vs. 0.89 days). Societal costs were increased 2.38-fold (£46.87 vs. £18.53) in the ED group.

Table 28: Breakdown of cost-types per patient in the GP and ED treatment groups

	GP (n=8404)	ED (n=4695)	Difference	Significance*
Staff salaries	£82.81	£46	£36.81	p<0.001
Observation/Inpatient	£28.86	£89.28	-£60.42	p<0.001
Prescribed medications	£3.09	£3.29	-£0.20	p=0.385
Investigations	£0.43	£2.77	-£2.34	p<0.001
Societal[#]	£19.69	£46.87	-£28.34	p<0.001

**Mann Whitney U-test*

 # Calculated as a function of total time in the ED, expressed in terms of the potential for forgone wages and/or productivity by parents and carers.

Sub-group analyses

Age of the child

While children aged <6 months and greater than 11 years were the most expensive to treat overall (Table 29), children of all ages, except for those aged 6-12 months, experienced lower costs of management if treated by the GP. This reached a maximum among those aged <3 months, where children managed as part of the GP group exhibited a £143.05 cost reduction per child compared to those in the ED group. Additionally, antibiotic prescribing was statistically significantly higher in the GP group for all children aged >6 months. Inpatient admission and achievement of the Department of Health's four-hour standard were not affected by age of the child.

Deprivation status

There was no difference in deprivation scores across treatment groups, as demonstrated within Table 25 (p=0.656). Deprivation was not associated with increased treatment costs or inpatient admission, however children managed by the GP in the most deprived groups (IMD quintiles 1-3) were significantly more likely to receive antibiotics than those managed by ED clinicians, as shown in Table 30 (all p<0.05).

Fever

Table 29: Treatment costs differentiated by aetiology of fever and treatment group

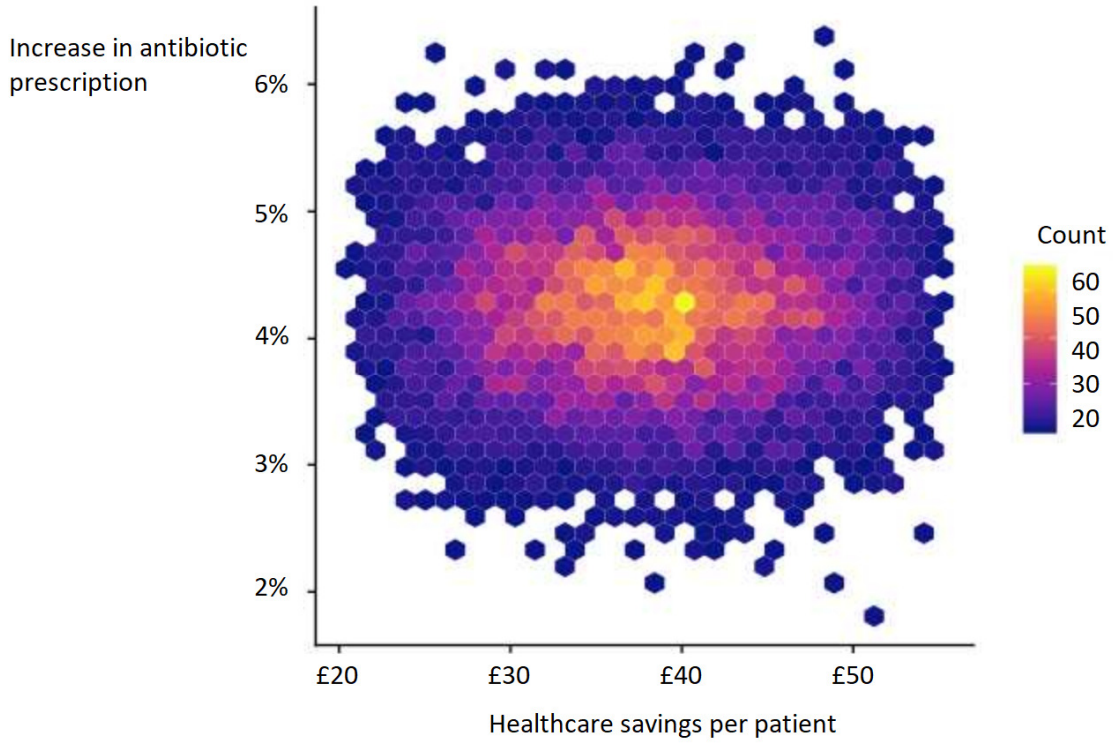
	GP Group	**ED Group**	**Significance**
Unknown bacterial or viral (n=1,518)	£89.32	£67.27	p<0.0001
Probable Viral (n=19)	N/A	£205.25	N/A*
Definite Viral (n=5)	£3,426.87	£525.09	p=0.1573
Viral Syndrome (n=93)	£105.50	£65.77	p<0.0001
All Viral (n=117)	£163.77	£140.56	p=0.0032
Probable Bacterial (n=2)	N/A	£846.12	N/A*
Definite Bacterial (n=35)	£166.25	£133.70	p=0.0001
Bacterial Syndrome (n=95)	£96.89	£60.22	p<0.0001
All Bacterial (n=132)	£107.99	£117.45	p<0.0001
Other infection (n=120)	£90.96	£37.48	p<0.0001
Trivial (n=13)	£87.19	£47.24	p=0.0266
Inflammation (n=7)	£85.02	£48.62	p=0.1037

Sensitivity analysis

Probabilistic sensitivity analysis utilising the distributions provided in Table 24, suggested an 86% probability that GP-led care would result in a saving of at least £30 per patient, when compared to management by ED teams. Similarly, there was a 98.3%

probability that treatment by GPs in the ED would increase antibiotic prescribing by at least 3% in absolute terms (Figure 29).

Figure 29: Variability in health service savings and antibiotic use following introduction of GP to ED



**Each hexagon represents a point in the joint distribution of paired healthcare savings and increases in antibiotic use, resulting from 10,000 Monte Carlo simulations. The colour represents the frequency/likelihood of each pairing occurring.*

Table 30: Comparative costs and outcomes by sub-group

	Healthcare costs				Antibiotics				Inpatient admission			
	GP	**ED**	**All**	**Sig.**	**GP**	**ED**	**All**	**Sig.**	**GP**	**ED**	**All**	**Sig**
Working diagnosis												
Fever (n=1,926)	£93.78	£69.76	£86.69	p<0.001	27.1%	16.7%	23.5%	p<0.001	1.1%	4.5%	2.3%	p<0.001
Infectious Disease (n=1,889)	£92.18	£123.29	£103.94	p<0.001	5.7%	5.9%	5.7%	p=0.578	0.7%	9.9%	4.4%	p<0.001
Gastrointestinal (n=2,105)	£89.49	£120.77	£104.76	p<0.001	0.5%	0.6%	0.6%	p=0.891	1.0%	8.6%	3.9%	p<0.001
Respiratory (n=3,146)	£87.52	£89.40	£88.16	p=0.897	16.2%	10.2%	14.3%	p<0.001	0.5%	6.5%	2.7%	p<0.001
Local Infection (n=866)	£92.97	£88.26	£91.34	p=0.521	40.3%	39.9%	40.2%	p=0.978	0.7%	4.1%	2%	p<0.001
Ear, Nose and Throat (n=906)	£86.78	£111.90	£92.30	p<0.001	41.5%	35.7%	40.1%	p=0.298	0.0%	2.8%	0.7%	p<0.001
Age												
<3 months (n=932)	£99.49	£242.54	£152.88	p<0.001	5.2%	5.6%	5.4%	p=0.947	1.2%	14.3%	6.2%	p<0.001
3-6 months (n=829)	£135.55	£196.38	£162.38	p<0.001	8.8%	8.2%	8.6%	p=0.935	2.3%	7.1%	4.5%	p<0.001
6-12 months (n=1,991)	£101.04	£95.29	£100.60	p<0.001	13.1%	8.6%	11.5%	p=0.012	1.6%	7.8%	4.2%	p<0.001
1-3 years (n=4,956)	£99.83	£116.47	£109.70	p<0.001	18.2%	11.5%	15.7%	p<0.001	1.1%	7.1%	3.6%	p<0.001
4-10 years (n=3,191)	£118.36	£130.14	£132.08	p<0.001	16.8%	13.4%	15.5%	p=0.037	1.4%	5.7%	3.3%	p<0.001
11+ years (n=1,200)	£115.39	£238.72	£157.93	p<0.001	13.9%	10.4%	12.9%	p=0.07	1.6%	7.7%	3.9%	p<0.001
Deprivation quintile#												
1 (n=8,436)	£111.56	£150.61	£126.23	p<0.001	15.40%	10.30%	13.50%	p<0.001	1.40%	7.80%	3.80%	p<0.001
2 (n=1,426)	£108.43	£150.48	£124.33	p<0.001	16.60%	11.50%	14.70%	p=0.009	1.20%	8.90%	4.20%	p=0.003
3 (n=1,337)	£94.17	£170.70	£124.10	p<0.001	14.80%	11%	13.30%	p=0.047	1.70%	7.70%	4%	p<0.001
4 (n=709)	£104.17	£92.69	£99.98	p<0.001	12.70%	12.90%	12.80%	p=0921	1.50%	5.70%	3.10%	p<0.001
5 (n=314)	£115.55	£189.99	£141.29	p<0.001	14.90%	17.30%	15.70%	p=0.582	1.40%	10.90%	4.70%	p<0.001

** Significance determined via Mann Whitney U-test*

 # 1 (most deprived), 5 least deprived)

Discussion

Summary of principal findings

During a two-year natural experiment in which a GP service was co-located in a busy paediatric ED for non-urgent admissions; treatment by the GP was associated with reductions in treatment costs, admittance to hospital, and in the number exceeding the 4-hour waiting target, but increases in antimicrobial prescribing. These findings corroborate those of a previous much smaller study, which did not include a health-economic analysis (Smith, et al. 2018).

Strengths & limitations of the chapter

To the best of our knowledge, this study, conducted among a large and representative ED cohort over a two-year period, is the first to assess the combined clinical, process-based and economic impact of introducing a GP service within a paediatric ED in the UK. The chapter makes use of a natural experiment, and routinely collected data, to pragmatically evaluate the impact of GP co-location in one of Europe's largest and busiest specialist paediatric EDs. Although this was a retrospective observational study, there were no significant differences in demographics and case mix between treatment groups, which have been previously shown to affect the outcomes under consideration (Leigh, Grant, et al. 2018). This limited the likelihood of confounding bias, thereby providing generalisable insights regarding the management of non-urgent presentations to EDs. Furthermore, although observational, the approach taken to the estimation of costs was highly thorough and representative of real-world

management, including details such as nursing time required to prepare and provide medications, and clinical time required to order and interpret investigations.

This chapter also has several limitations. Firstly, we did not collect data on several factors which may have affected both ED and GP staff workload, including how busy the department was at any given time, the number of staff on-shift, and the availability and capacity of connected departments, such as pathology and radiology, which may have affected the ability of GPs and ED clinicians to treat and investigate the children included efficiently. Secondly, despite 91% of the patients having complete data to enable analysis, there was a significant difference in complete data capture between the two treatment groups, which may also have impacted the findings of the chapter. For those in the GP-led management group just 303 from a potential 8,707 cases had incomplete data (3.5%), such that analysis of healthcare costs was not possible without relying on assumptions. Conversely, in the ED treatment group a total of 1,042 out of a possible 5,737 unique cases were missing data critical to the assessment of healthcare costs, representing 18.2% of this group. Rates of non-inclusion for ED patients were largely as a result of the computer system used, and the process for inputting patient data. The process for ED patients usually involves a clinician filling in notes using a computer system, post discharge, leaving the possibility that if case-load increases and patients are in need of acute medical attention, clinicians will not complete administrative work. By comparison, given that the GPs on site in the ED focus exclusively on non-urgent cases, the likelihood of failing to complete patient discharge notes on account of unplanned emergency medical intervention is significantly lower.

Thirdly, although every effort was made to eliminate sources of bias, including the large patient numbers and balanced baseline characteristics, the retrospective nature of the study, and lack of randomisation does leave the opportunity for unknown causes of bias, which could not be adjusted for. Additionally, we used net-ingredient costs provided by the NHS to estimate the prices paid by NHS providers for various components of the pathways detailed in this Chapter. However, these costs represent baseline costs prior to the negotiation of discounts by Trusts, suggesting the findings presented likely over-estimate the financial cost of consumables and diagnostics. While this data detailing the precise costs of the consumables and diagnostics used were not publicly available, this remains a limitation as any discounts achieved effectively lower the price of managing the condition. Finally, although higher rates of incomplete data capture and exclusion were observed for the ED group, we believe it is unlikely that this impacted the findings of the chapter. Missing data seem to be missing at random in verification samples and they appear to occur during busy times and related to the electronic system used. Yet, inevitably, we cannot confirm this with certainty, nor determine how these patients would have affected the detailed findings of the study if they were included in the analysis.

Comparison with existing literature

Prior interventional analyses and systematic reviews have suggested that co-location of GPs in EDs may not have a significant impact on reducing the cost per patient seen (Ramlakhan, Mason and O'Keeffe 2016), but may in fact increase costs due to extra personnel (Salisbury, Hollinghurst and Montgomery 2007). The findings of this chapter, in the largest cohort to date, suggest otherwise. Despite personnel costs

increasing, non-urgent children managed by GPs experienced significant reductions in total costs of management, predominantly resulting from reductions in inpatient admission, investigations, and radiography; as observed in similar studies (Khangura, Flodgren and Perera 2012) (Kool, Homberg and Kamphuis 2008). This difference was most pronounced among younger children, where healthcare costs were reduced by almost 60%, and where understandably, ED staff are known to be most cautious (Leigh, Grant, et al. 2018).

In EDs which are frequently overcrowded, the significant reduction in activities associated with waiting (observation, investigations, radiography) as observed in the GP group, may have a significant effect on patient flow through the ED, resulting in reductions in waiting times and increases in patient satisfaction. This could have significant implications for NHS trusts, as breaching the target of resolving at least 95% of the attendances within 4 hours can have serious negative economic consequences for hospitals (The-Kings-Fund 2013). The increase in achievement of the four-hour standard from 88.4% in the ED group to 98.6% in the GP group, therefore also has the potential to save NHS trusts money in the short to medium term which were not captured in this analysis. However, a potential limitation, observed in both this study and the previously published pilot study (Smith, et al. 2018), is that a substantial number of patients managed by GPs were subsequently referred to their own GP for further follow-up; which may simply shift some of the burden to primary care. As such, the impact on the whole system of GP in the ED models of care still requires further investigation.

Finally, although GP-led care for non-urgent attendances resulted in several significant benefits, the resulting increase in antibiotic prescription was also significant. There are considerable clinical policy pressures on GPs not to miss sepsis, meningitis, or other serious-but-rare illnesses, often a result of diagnostic uncertainty (Leigh, Grant, et al. 2018), which may push practitioners to prescribe as a precaution (Limper, et al. 2011) (Wilkes, et al. 2009). A previous study found that 44% of GPs might prescribe antibiotics to terminate a consultation (Cole 2014), and implicit in this finding is the potential effect of the increasingly tight time constraints under which GPs work, and the number of children seen over relatively short periods of time. In this study, children who were managed by the GP who were seen and discharged within one-hour were three times more likely to be prescribed antibiotics, compared to children seen and discharged within a similar period who were managed by ED clinicians. Consultation time and GP workload have been shown to be associated with higher antibiotic prescription rates (Williams, Halls and Tonkin-Crine 2018), and it is worth noting that in this study, the GP managed almost twice as many non-urgent cases as ED clinicians over the same period. In Norway, a study found that GPs who saw more patients per year prescribed more antibiotics than those with fewer patients (Gjelstad, Straand and Dalen 2011), and this was echoed in a qualitative study of GPs and nurse prescribers in the UK (Jabaley, Blum and Groff 2018).

Advances in diagnostic technologies such as rapid POC testing may play a role in reducing potentially avoidable antibiotic prescribing. POC CRP testing has been shown to reduce antibiotic prescribing in UK primary care clinics for patients with COPD (Butler, Gillespie and White 2019). Community antibiotic stewardship by

pharmacists (Saha, Hawes and Mazza 2019), and continued evolution of the GP in the ED model to include pharmacists in the ED, who are frequently faced with patients presenting with minor illnesses, would represent a valuable addition to the research base on this subject. Pharmacists may have different views on AMR and antimicrobial prescribing than both GPs and ED teams. Prior research has demonstrated that the presence of pharmacists in the ED can increase guideline-concordant prescribing significantly (Kulwicki, et al. 2019) and given that pharmacists are increasingly seen in paediatric EDs, additional research on how this model of care may impact the outcomes considered in this study, not solely limited to antimicrobial prescribing, would be of significant value. Similarly, prior studies have also suggested prescribing or social norm feedback as part of continued GP education (Williams, Halls and Tonkin-Crine 2018) (Hallsworth, Chadborn and Sallis 2016), or primary care accreditation schemes (van der Velden, Kuyvenhoven and Verheij 2016), as means of reducing antimicrobial prescribing. Given the success of these initiatives in reducing antibiotic use in routine practice, coupled with low expected costs of implementation and GPs being easily accessible in a single hospital setting, there is every possibility to reduce antibiotic use.

Chapter 5 summary

The aim of this chapter was to follow up on the findings of the previous, which demonstrated a clear emphasis on the importance of minimising waiting times for those attending the ED due to paediatric febrile illness. Given the increasing demands on emergency care, integrative care approaches have been suggested a plausible means of increasing capacity and managing caseloads caseload, particularly given the non-

urgent nature of many attendees. This may improve not only the experiences of those receiving care from GPs, but also others managed by ED teams who experience a reduced waiting time as a result. The aim of this chapter was therefore to assess whether this model of care may be of benefit from an operational, clinical, and economic perspective, when considering non-urgent ED presentations including paediatric febrile illness. The published peer reviewed version of this chapter is provided in Appendix 1 below.

The findings of this chapter, a large-scale natural experiment, suggest that co-locating a GP in paediatric EDs is likely to reduce waiting times, inpatient admissions, and treatment costs significantly. In the context of chapters three and four, this represents a potential improvement, with both economic costs and satisfaction with care improving as waiting times, and the use of invasive and often clinically unnecessary invasive investigations decreases. However, the results of this chapter demonstrate that this benefit is likely to come at a cost, an increase in antibiotic prescribing. In the context of paediatric febrile illness, this may be problematic given the already high rates of antimicrobial prescribing experienced within a group which will predominantly be experiencing self-limiting and often clinically benign viral illnesses. While our results demonstrate that the inclusion of GPs in EDs can be expected to reduce the pressure on frontline services, thereby freeing resources to treat more urgent cases, they would likely need to be accompanied by effective strategies for antimicrobial stewardship or diagnostic improvements which can reduce reliance on antimicrobials among GP-treated patients. The next chapter of this thesis explores this theme further, building upon the findings of all previous chapters combined. Using

economic evaluation techniques, the economic costs, parental & HCP satisfaction with care, and antimicrobial prescribing rates associated with several care pathways for the ED-management of paediatric febrile illness will be explored. In doing so the aim of this final chapter is to determine the overall value of modifying care processes for managing paediatric febrile illness in ED settings.

Chapter 5 Appendix

Appendix 1 – Published manuscript

Simon Leigh, Bimal Mehta, Lillian Dummer, Harriet Aird, Sinead McSorley, Venessa Oseyenum, Anna Cumbers, Mary Ryan, Karl Edwardson, Phil Johnston, Jude Robinson, Frans Coenen, David Taylor-Robinson, Louis W Niessen and Enitan D Carrol

Management of non-urgent paediatric emergency department attendances by GPs:

a retrospective observational study

Abstract

Background
Non-urgent emergency department (ED) attendances are common among children. Primary care management may not only be more clinically appropriate, but may also improve patient experience and be more cost-effective.

Aim
To determine the impact on admissions, waiting times, antibiotic prescribing, and treatment costs of integrating a GP into a paediatric ED.

Design and setting
Retrospective cohort study explored non-urgent ED presentations in a paediatric ED in north-west England.

Method
From 1 October 2015 to 30 September 2017, a GP was situated in the ED from 2.00 pm until 10.00 pm, 7 days a week. All children triaged as 'green' using the Manchester Triage System (non-urgent) were considered to be 'GP appropriate'. In cases of GP non-availability, children considered non-urgent were managed by ED staff. Clinical and operational outcomes, as well as the healthcare costs of children managed by GPs and ED staff across the same timeframe over a 2-year period were compared.

Results
Of 115 000 children attending the ED over the study period, a complete set of data were available for 13 099 categorised as 'GP appropriate'; of these, 8404 (64.2%) were managed by GPs and 4695 (35.8%) by ED staff. Median duration of ED stay was 39 min (interquartile range [IQR] 16–108 min) in the GP group and 165 min (IQR 104–222 min) in the ED group ($P<0.001$). Children in the GP group were less likely to be admitted as inpatients (odds ratio [OR] 0.16; 95% confidence interval [CI] = 0.13 to 0.20) and less likely to wait >4 hours before being admitted or discharged (OR 0.11; 95% CI = 0.08 to 0.13), but were more likely to receive antibiotics (OR 1.42; 95% CI = 1.27 to 1.58). Treatment costs were 18.4% lower in the group managed by the GP ($P<0.0001$).

Conclusion
Given the rising demand for children's emergency services, GP in ED care models may improve the management of non-urgent ED presentations. However, further research that incorporates causative study designs is required.

Keywords
antibiotics; cost-effectiveness; emergency care; paediatrics; primary care.

INTRODUCTION

The total number of visits to emergency departments (EDs) in England exceeded 24 million in 2018[1] and has risen by 42% since 2008,[2] with over two-thirds of attendances taking place without GP referral or transfer by ambulance.[3] Although these attendances may result from an acute medical problem, they may not always require immediate, specialised emergency medical care, with 20%–40% of ED visits having been classified as non-urgent.[4,5] Increased concern regarding the potential severity of conditions,[6] parental anxiety,[7] and a perceived need for urgent treatment[7–10] exacerbate this problem in children's emergency medicine. Confidence in the quality and investigative ability of ED care,[7] as well as difficulty obtaining primary care appointments,[11] also plays a role; as such, it is estimated that one in two attendances for acute paediatric care could feasibly be managed in the community.[12]

A major challenge for staff in paediatric emergency care is to recognise children who are seriously ill, and the increasing use of EDs for non-urgent conditions makes this difficult; ED overcrowding is a major patient safety concern,[13,14] which can result in suboptimal patient outcomes and even death.[15,16]

Given that an increasing number of non-urgent ED attendances are amenable to treatment in primary care, one of the key recommendations of a joint report published by the College of Emergency Medicine, Royal College of Paediatrics and Child Health, Royal College of Physicians, and Royal College of Surgeons is to co-locate primary care services within ED settings.[17] Although the benefits of introducing GPs into EDs for managing non-urgent cases are well documented and include increased patient satisfaction,[18–20] reduced waiting times,[19] and reductions in invasive examinations,[21] it is unclear whether this represents an efficient use of NHS resources, with the only economic analysis to date taking place in 1996.[22] Building on the authors' previous findings from a 6-month pilot scheme of the initiative,[19] which assessed clinical and process outcomes, this retrospective observational study, conducted in one of Europe's largest and busiest specialist paediatric EDs, assesses the impact of a primary care service located in an ED on waiting times, admissions, antibiotic prescribing rates, and healthcare costs. The aim was to determine the cost-effectiveness of the ED co-location of GP services.

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How this fits in

Many emergency department (ED) attendances are non-urgent, putting pressure on services and increasing caseloads. Having a GP available in the ED to manage non-urgent cases has previously been shown to improve efficiency and patient satisfaction, but it is unclear whether this demonstrates value for money. This large, non-randomised, observational study shows that children seen by the GP in the ED waited less time to be seen, had fewer inpatient admissions, and incurred lower healthcare costs, but experienced higher antibiotic prescribing than those managed by ED teams. As the demand for children's emergency services is increasing, having a GP present in the ED may have a positive effect on how non-urgent paediatric cases are managed. Further research is, however, required.

METHOD

Study setting, population, and design

The study was conducted retrospectively in the ED of a large paediatric hospital located in the north-west of England. From 1 October 2015 until 30 September 2017, a GP employed by a Liverpool-based social enterprise delivering NHS services (Primary Care 24, formerly Urgent Care 24) was available in the ED as a separate but co-located service. The service ran from 2.00 pm until 10.00 pm, 7 days a week.

All children were initially evaluated by a qualified ED nurse using the Manchester Triage System (MTS).[23] Low-acuity children triaged as non-urgent (categorised as MTS green without comorbidities) were labelled 'GP appropriate' and allocated to be seen by the GP during the operational hours of 2.00 pm–10.00 pm. Parents were not given a choice of allocation to the GP or otherwise but were informed of the decision, at which point they could refuse the service. Children referred to the ED by their own GP or a walk-in centre were ineligible for allocation to the GP in the ED service.

In instances of GP non-availability — namely, GP sickness — children triaged as 'GP appropriate', who would otherwise have been managed by onsite GPs, were instead managed by ED clinical staff, following the standard procedures of the service (the comparator group). This intervention presented an opportunity to evaluate a natural experiment, comparing both outcomes — antimicrobial prescribing, wait times (and achievement of the Department of Health and Social Care's 4-hour target), and admission rates — and costs of children presenting to the paediatric ED with the same clinical urgency (MTS green) over the same time period (2.00 pm–10.00 pm, 7 days a week), differing only in terms of whether treatment was provided by ED teams or the co-located GP service. The study recruitment process is outlined in Figure 1.

Due to the retrospective observational nature of the study, in addition to primary outcome data, data concerning potential confounders were collected for all patients from both ED and GP service databases. For all cases, the following information were available:

- arrival and discharge date and time;
- final diagnosis;
- discharge status;
- antimicrobial prescribing; and
- attending physician.

Demographic data (age, sex, home postcode, and Index of Multiple Deprivation 2015 score) and clinical data (oxygen saturation, temperature, and pulse) were also collected. For those patients presenting with fever who received antibiotics, an assessment of whether antibiotic prescribing was clinically necessary was made, based on the retrospective application of an adapted

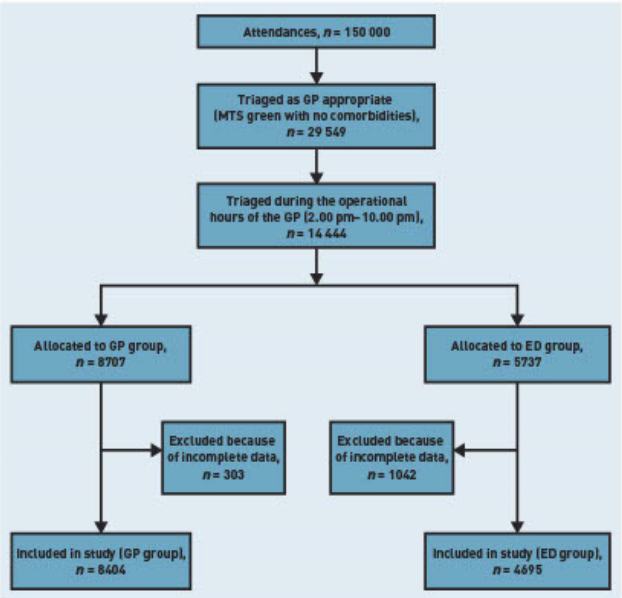

Figure 1. Study recruitment process. ED = emergency department. MTS = Manchester Triage System.

algorithm from Herberg *et al*,[24] details of which are provided in Supplementary Box S1.

Statistical analysis

Patients triaged as 'GP appropriate' and managed by the GP service (exposed group) were compared with patients triaged as 'GP appropriate' and managed by ED staff over the same time period (control group), using an intention-to-treat approach. Descriptive statistics were generated for both groups. Differences in proportions were analysed using the χ^2 test, with differences in continuous outcomes assessed via the Mann–Whitney *U* test. Multivariate logistic regression was used to estimate odds ratios (ORs) for binary outcomes, adjusted for baseline covariates that may have impacted outcomes, including whether children were re-attending the ED within a 5-day period or whether they had previously sought care from their community GP. Subgroup analyses were performed to account for covariates previously shown to impact the outcomes under consideration, including patient age,[25] working diagnosis,[25] and deprivation.[26] All statistical analyses were conducted using Stata (version 12), with statistical significance defined at the 5% level.

Costing and resource-use analysis

Healthcare resource use was calculated using a time-driven, activity-based costing (TDABC) approach, as used in previous health economic analyses conducted in the ED.[25] TDABC identifies all instances and durations of interaction with health service personnel during a treatment episode and assigns time-dependent costs to each (triage, consultation, cannulation, and so on), based on stopwatch timing combined with the hourly salaries of the staff involved. Timing estimates and unit costs that were used for the patient-level healthcare costing are provided in Supplementary Tables S1 and S2. Finally, adding unit costs of consumables (including medicines) and tariff-based items (including investigations, radiography, and inpatient admission spells) provides an estimation of total resource use during a treatment episode. Further details of the methodology for the costing exercise are provided elsewhere.[25] Societal costs to parents of waiting in the ED were also estimated by cross-referencing each responder's postcode with hourly income data matched per lower layer super output area, which was obtained from the Office for National Statistics.[27]

All unit costs were in 2019 prices, with non-parametric bootstrapping (percentile method) used to generate 95% confidence intervals (CIs). Discounting of costs and outcomes was not required because of the short analysis timeframe. Probabilistic sensitivity analysis was also performed to test for robustness of conclusions regarding the impact of GP-led care on healthcare costs and outcomes. The distributions employed to explore parametric uncertainty are provided in Supplementary Table S3.

RESULTS

Baseline characteristics and recruitment

Between 1 October 2015 and 30 September 2017, 115 000 children visited the ED, of whom 14 444 were triaged as 'GP appropriate' (MTS green) between 2.00 pm and 10.00 pm, when the onsite GPs were in operation. Of these children, 1345 had incomplete or missing data, resulting in a cohort comprising 13 099 children. Table 1 shows the personal characteristics of those who were treated by a GP and those treated by ED staff; no statistically significant differences were observed in any of the demographic or clinical baseline characteristics.

Antibiotic prescribing

Rates of antibiotic prescribing were 15.1% in the GP group and 10.8% in the ED group (OR 1.42; 95% CI = 1.27 to 1.58; *P*<0.001) (see Supplementary Figure S1). Compared with children managed by ED teams, those managed by the GP who were seen and discharged within 1 hour had an OR of 3.32 (95% CI = 2.20 to 5.00) for being prescribed antibiotics. Children managed by the GP group who had fever at presentation experienced a 10.4% increase in antibiotic prescribing (27.1% versus 16.7%) (data not shown). Approximately 89.9% of children with fever receiving antibiotics in the GP group, compared with 75.9% in the ED group, displayed no evidence of bacterial foci (see Supplementary Table S4).

Wait times

The median duration of stay in the ED was 39 min (interquartile range (IQR) 16–108 min) for the GP group, compared with 165 min (IQR 104–222 min) for the ED group (*P*<0.005) (data not shown). Management by the onsite GP was associated with statistically significantly reduced odds of breaching the UK Department of Health and Social Care's 4-hour waiting standard (OR 0.10; 95% CI = 0.08 to 0.13; *P*<0.001); 98.6% of children in the GP group and 88.4% of those in the ED group were discharged or admitted within 4 hours (data not shown).

Table 1. Characteristics of patients triaged as 'GP appropriate', attending the emergency department

Variable	GP group, *N* = 8404	ED group, *N* = 4695	Total, *N* = 13 099	*P*-value
Sex, *n* (%)				0.206[a]
Male	4268 (50.8)	2541 (54.1)	6809 (52.0)	
Female	4136 (49.2)	2154 (45.9)	6290 (48.0)	
Age category, *n* (%)				0.785[a]
<3 months	613 (7.3)	319 (6.8)	932 (7.1)	
3–6 months	538 (6.4)	291 (6.2)	829 (6.3)	
7–12 months	1277 (15.2)	714 (15.2)	1991 (15.2)	
>1–3 years	3177 (37.8)	1779 (37.9)	4956 (37.8)	
4–10 years	2017 (24.0)	1174 (25.0)	3191 (24.4)	
≥11 years	782 (9.3)	418 (8.9)	1200 (9.2)	
Age, years, median (IQR)	2.2 (0.90–5.50)	2.15 (0.87–5.50)	2.17 (0.88–5.50)	0.624[b]
Deprivation quintiles, *n* (%)[c]				0.656[a]
1 (least deprived)	208 (2.5)	106 (2.3)	314 (2.4)	
2	456 (5.4)	253 (5.4)	709 (5.4)	
3	833 (9.9)	504 (10.7)	1337 (10.2)	
4	898 (10.7)	528 (11.2)	1426 (10.9)	
5 (most deprived)	5378 (64.0)	3058 (65.1)	8436 (64.4)	
Diagnosis, *n* (%)				n/a
Respiratory conditions	2070 (24.6)	1076 (22.9)	3146 (24.0)	
Gastrointestinal conditions	1410 (16.8)	695 (14.8)	2105 (16.1)	
Infectious disease	1194 (14.2)	695 (14.8)	1889 (14.4)	
Diagnosis not classifiable	530 (6.3)	946 (20.1)	1476 (11.3)	
ENT conditions	679 (8.1)	227 (4.8)	906 (6.9)	
Local infection	561 (6.7)	305 (6.5)	866 (6.6)	
Dermatological conditions	302 (3.6)	99 (2.1)	401 (3.1)	
Urological conditions (including cystitis)	256 (3.0)	128 (2.7)	384 (2.9)	
Allergy (including anaphylaxis)	263 (3.1)	100 (2.1)	363 (2.8)	
Head injury	190 (2.3)	45 (1.0)	235 (1.8)	
Fever	1289 (15.3)	643 (13.7)	1932 (14.7)	
Pulse, beats/minute, median (IQR)	127 (109–143)	125 (109–140)	126 (109–142)	0.864[b]
Temperature, °C, median (IQR)	37 (36.6–37.6)	37 (36.6–37.6)	37 (36.6–37.6)	0.767[b]
Oxygen saturation, %, median (IQR)	99 (97–100)	99 (97–100)	99 (97–100)	0.558[b]
Attended ED in last 5 days, *n* (%)				0.14[a]
Yes	160 (1.9)	103 (2.2)	263 (2.0)	
No	8244 (98.1)	4592 (97.8)	12 836 (98.0)	
Attended ED on a weekday, *n* (%)				0.84[a]
Yes	5824 (69.3)	3301 (70.3)	9125 (69.7)	
No	2580 (30.7)	1394 (29.7)	3974 (30.3)	
Attended ED during holiday period, *n* (%)[d]				0.134[a]
Yes	2958 (35.2)	1592 (33.9)	4550 (34.7)	
No	5446 (64.8)	3103 (66.1)	8549 (65.3)	

[a]χ^2. [b]Mann–Whitney U test. [c]Deprivation data were based on postcodes. Many of the children attending the ED either had no postcode on file, incomplete postcodes, or were classed as Travellers, with postcodes that did not link to the Office for National Statistics database. N-values for GP group, ED group, and Total are 7773, 4449, and 12 222, respectively. [d]Holidays were in line with the English academic year and included half terms, Easter, Christmas, and winter holidays. ED = emergency department. ENT = ear, nose, and throat. IQR = interquartile range.

Admission to hospital and discharge status

The odds of being admitted were statistically significantly lower (84.0%) for children managed by the GP (OR 0.16; 95% CI = 0.13 to 0.20; *P*<0.001) than those managed by ED staff (data not shown). Short-stay admissions of <6 hours were reduced by 84.7%, 6–24-hour admissions by 86.5%, and admissions exceeding 24 hours by 78.7% for those seen by the GP, when compared with the group managed by ED staff. Children in all age groups and all diagnostic groups were statistically significantly more likely to be admitted to hospital if managed by ED clinical teams (all *P*<0.001) (data not shown). The grade of the ED clinician

Table 2. Discharge status of children by treatment group

Discharge status	GP group,[a] *n* (%)	ED group,[b] *n* (%)	Total,[c] *n* (%)
Own GP follow-up	2312 (27.5)	287 (6.1)	2599 (19.8)
Discharged with no further action	5745 (68.4)	3282 (69.9)	9027 (68.9)
Admitted	117 (1.4)	374 (8.0)	491 (3.7)
Outpatient	107 (1.3)	103 (2.2)	210 (1.6)
ED clinic	3 (<0.1)	59 (1.3)	62 (0.5)
Community follow-up	1 (<0.1)	0 (0.0)	1 (<0.1)
Left before seen	100 (1.2)	455 (9.7)	555 (4.2)
Left following advice	1 (<0.1)	5 (0.1)	6 (<0.1)
Left refusing treatment	6 (0.1)	117 (2.5)	123 (0.9)
Other	5 (0.1)	13 (0.3)	18 (0.1)
N/A	7 (0.1)	0 (0.0)	7 (0.1)

[a]N = 8404. [b]N = 4695. [c]N = 13 099. *ED = emergency department.*

managing the child had no impact on admission rates (data not shown).

In total, 95.9% of children in the GP group were discharged with no further action or advised to seek follow-up with their own GP, compared with 76.0% in the ED group (Table 2). Outpatient referrals were equivalent across groups, with 107 (1.3%) children in the GP group and 103 (2.2%) children in the ED group referred, but 9.7% of children in the ED group left the ED before being seen, compared with 1.2% in the GP group (Table 2).

Healthcare and societal costs of ED management

The mean cost of treatment episodes for the GP group was 115.24 GBP (95% CI = 20.50 to 351.67 GBP), compared with 141.16 GBP (95% CI = 11.78 to 539.94 GBP) among those managed by ED clinicians (P<0.001) (data not shown). Both groups recorded similar costs attributable to medications prescribing, and investigations (Table 3). Costs associated with staff salaries (receptionist, nurse, and doctor) were much higher in the GP group than in the ED group, but inpatient admission costs were statistically significantly lower (P<0.001) (Table 3); this owed primarily to a 75.3% reduction in median inpatient duration (0.22 days versus 0.89 days) (data not shown). Societal costs were increased by 27.18 (46.87 versus 19.69 GBP) in the ED group, compared with the GP group (Table 3).

Subgroup analyses

Subgroup analyses for all outcomes are provided in Table 4 and Supplementary Box S2.

Sensitivity analysis

Probabilistic sensitivity analysis utilising the distributions provided in Supplementary Table S3 suggested an 86.0% probability that GP-led care would result in a saving of at least 30 GBP per patient. Similarly, there was a 98.3% probability that treatment by GPs in the ED would increase antibiotic prescribing by at least 3% (Figure 2).

DISCUSSION

Summary

During a 2-year natural experiment, in which a GP service was co-located in a busy paediatric ED for non-urgent admissions, patients being managed by GPs instead of ED staff resulted in lower treatment costs, fewer hospital admissions, and fewer patients exceeding the 4-hour waiting target; however, those seen by the GP were subject to higher rates of antimicrobial prescribing.

Strengths and limitations

To the best of the authors' knowledge, the study presented here, conducted among a large and representative ED cohort over a 2-year period, is the first to assess the combined clinical, process-based, and economic impact of introducing a GP service to a paediatric ED in the UK. The authors have made use of a natural experiment and routinely collected data to pragmatically evaluate the impact of GP co-location in one of Europe's largest and busiest specialist paediatric EDs. Although this was a retrospective observational study, the treatment groups were almost identical in terms of demographics and case mix, which have been previously shown to affect the outcomes under consideration.[25] This

Table 3. Breakdown of cost types per patient in the GP and ED treatment groups

Cost type	Costs, GBP			*P*-value[a]
	GP group	ED group	Difference	
Staff salaries	82.81	46.00	36.81	0.001
Observation/inpatient	28.86	89.28	60.42	0.001
Prescribed medications	3.09	3.29	0.20	0.385
Investigations	0.43	2.77	2.34	0.001
Societal[b]	19.69	46.87	27.18	0.001

[a] Mann–Whitney U test. [b] Calculated as a function of total time in the ED, expressed in terms of forgone wages and productivity by parents and carers. ED = emergency department. GBP = Great British pound.

limited the likelihood of confounding bias, thereby providing generalisable insights regarding the management of non-urgent presentations to EDs. Furthermore, although observational, the approach taken to estimate costs was highly thorough and representative of real-world management, including details such as nursing time required to prepare and provide medications, and clinical time required to order and interpret investigations.

The study presented here does have some limitations. The authors did not collect data on several factors that may have affected both ED and GP staff workload, including: how busy the department was at any given time; the number of staff on shift; and the availability and capacity of connected departments, such as pathology and radiology, which may have affected the ability for GPs and ED clinicians to treat and investigate the children included efficiently. In addition, although every effort was made to eliminate sources of bias, including the large patient numbers and subsequently balanced baseline characteristics, the retrospective nature of the study and lack of randomisation does leave the opportunity for unknown causes of bias that could not be adjusted for.

Higher rates of incomplete data capture and exclusion for the ED group very likely did not impact the findings. These seemed to be missing at random in verification samples; however, the authors can neither confirm this with certainty, nor determine how these patients would have affected the detailed findings of the study.

Finally, the fact that the operational hours of the GP service only covered a third of the operating hours of the ED (2.00 pm–10.00 pm) means that generalisability of the findings could be limited as it cannot be guaranteed that similar patterns of care would be observed overnight when services, diagnostics, and access to radiography are limited.

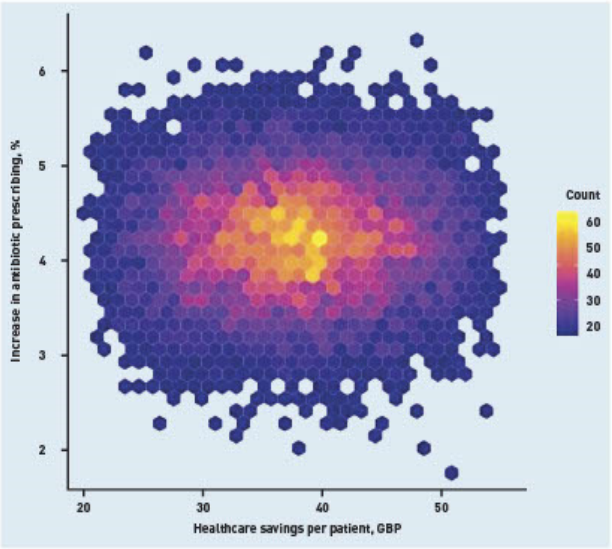

Figure 2. Variability in health service savings and antibiotic use following introduction of GP to emergency department.
Count = number of Monte Carlo simulations in which the cross-section of the x- and y-axis occurred. GBP = Great British Pound.

Comparison with existing literature

Prior interventional analyses and systematic reviews have suggested that the co-location of GPs in EDs may not have a significant impact on reducing the cost of care per patient[28,29] but may, in fact, increase costs because of extra personnel.[29] However, the findings presented here — in the largest cohort to date of which the authors are aware — suggest otherwise. Despite personnel costs increasing, children requiring non-urgent health care managed by GPs experienced significant reductions in total costs of management, predominantly resulting from reductions in inpatient admission, investigations, and radiography; this has also been observed in similar studies.[21,22,30] This difference was most pronounced among younger children (aged <6 months), for whom healthcare costs were reduced by almost 60% and in whom, understandably, ED staff are known to be most cautious.[25]

In EDs that are frequently overcrowded, the significant reduction in activities associated with waiting (observation, investigations, and radiography) as observed in the GP group, may have a significant effect on patient flow through the ED, resulting in reductions in waiting times and increases in patient satisfaction. This could have major implications for

Table 4. Comparative costs per patient and outcomes by subgroup

Variable	Costs, GBP				Antibiotics, %			4-hour target, %			Inpatient, %		
	GP group	ED group	All	*P*-value	GP group	ED group	All	*P*-value	GP group	ED group	All	*P*-value	GP group	ED group	All	*P*-value
Working diagnosis																
Fever, *n* = 1926	93.78	69.76	86.69	<0.001	27.1	14.7	23.5	<0.001	98.5	87.5	94.6	<0.001	1.1	4.5	2.3	<0.001
Infectious disease, *n* = 1889	92.18	123.29	103.94	<0.001	5.7	5.9	5.7	0.578	98.7	89.1	94.7	<0.001	0.7	9.9	4.4	<0.001
Gastrointestinal, *n* = 2105	89.49	120.77	104.76	<0.001	0.5	0.6	0.6	0.891	98.8	86.2	94.4	<0.001	1.0	8.6	3.9	<0.001
Respiratory *n* = 3146	87.52	89.40	88.16	0.897	16.2	10.2	14.3	<0.001	98.9	86.3	94.3	<0.001	0.5	6.5	2.7	<0.001
Local infection, *n* = 866	92.97	88.26	91.34	0.521	40.3	39.9	40.2	0.978	98.4	86.4	93.9	<0.001	0.7	4.1	2.0	<0.001
ENT, *n* = 906	86.78	111.90	92.30	<0.001	41.5	35.7	40.1	0.298	97.8	86.8	95.0	<0.001	0.0	2.8	0.7	<0.001
Age																
<3 months, *n* = 932	99.49	242.54	152.88	<0.001	5.2	5.6	5.4	0.947	99.2	87.9	95.2	<0.001	1.2	14.3	6.2	<0.001
3–6 months, *n* = 829	135.55	196.38	162.88	<0.001	8.8	8.2	8.6	0.935	98.5	90.1	95.2	<0.001	2.3	7.1	4.5	<0.001
6–12 months, *n* = 1991	101.04	95.29	100.60	<0.001	13.1	8.6	11.5	0.012	98.4	89.5	94.4	<0.001	1.6	7.8	4.2	<0.001
1–3 years, *n* = 4956	99.83	116.47	109.70	<0.001	18.2	11.5	15.7	<0.001	98.6	87.6	94.2	<0.001	1.1	7.1	3.6	<0.001
4–10 years, *n* = 3191	118.36	130.14	132.08	<0.001	16.8	13.4	15.5	0.037	98.6	89.5	94.6	<0.001	1.4	5.7	3.3	<0.001
≥1 years, *n* = 1200	115.39	238.72	157.93	<0.001	13.9	10.4	12.9	0.07	98.5	86.0	93.8	<0.001	1.6	7.7	3.9	<0.001
Deprivation quintile																
1 (most deprived, *n* = 8436	111.56	150.61	126.23	<0.001	15.4	10.3	13.5	<0.001	98.6	87.3	94.3	0.005	1.4	7.8	3.8	<0.001
2, *n* = 1426	108.43	150.48	124.33	<0.001	16.6	11.5	14.7	0.009	99.4	88.6	95.4	<0.001	1.2	8.9	4.2	0.003
3, *n* = 1337	94.17	170.70	124.10	<0.001	14.8	11.0	13.3	0.047	98.3	88.8	94.6	<0.001	1.7	7.7	4.0	<0.001
4, *n* = 709	104.17	92.69	99.98	<0.001	12.7	12.9	12.8	0.921	98.2	88.9	94.8	<0.001	1.5	5.7	3.1	<0.001
5 (least deprived), *n* = 314	115.55	189.99	141.29	<0.001	14.9	17.3	15.7	0.382	97.6	89.1	94.7	<0.001	1.4	10.9	4.7	<0.001

*Significance determined via Mann–Whitney U test. ED = emergency department. ENT = ear, nose, and throat. GBP = Great British pound.

NHS trusts, as breaching the target of resolving at least 95% of the attendances within 4 hours can have serious negative economic consequences for hospitals.[31] The increase in achievement of the 4-hour standard from 88.4% in the ED group to 98.6% in the GP group, therefore, also has the potential to save NHS trusts money in the short-to-medium term — possible savings that were not captured in this analysis. However, a potential limitation, observed in both this study and the authors' previously published pilot study,[19] is that a substantial number of patients managed by GPs were subsequently referred to their own GP for further follow-up; this may simply shift some of the burden to primary care. As such, the impact on the whole system of GP in the ED models of care still requires further investigation.

Finally, although GP-led care for non-urgent attendances resulted in several statistically significant benefits, the resulting increase in antibiotic prescription was also statistically significant. There are considerable clinical policy pressures on GPs not to miss sepsis, meningitis, or other illnesses that are serious but rare, often a result of diagnostic uncertainty,[25] which may push practitioners to prescribe as a precaution.[25,32,33] A previous study found that 44% of GPs might prescribe antibiotics to terminate a consultation;[34] implicit in this finding is the potential effect of the increasingly tight time constraints under which GPs work, and the number of children seen over relatively short periods of time. Findings in relation to patients seen by a GP receiving higher rates of microbial prescribing corroborate those of the authors' previous and much smaller study, which did not include a health economic analysis.[19] In the study presented here, children managed by the GP who were seen and discharged within 1 hour were three times more likely to be prescribed antibiotics, compared with children seen and discharged within a similar period who were managed by ED clinicians. Consultation time and GP workload have been shown to be associated with higher antibiotic prescription rates[35] and it is worth noting that, in this study, the GP managed almost twice as many non-urgent cases as ED clinicians over the same period. In Norway, a study found that GPs who saw more patients per year prescribed more antibiotics than those with fewer patients;[34] this was echoed in a qualitative study of GPs and nurse prescribers in the UK.[35]

Advances in diagnostic technologies, such as rapid point-of-care (POC) testing,

may play a role in reducing unnecessary antibiotic prescribing. POC C-reactive protein testing has been shown to reduce antibiotic prescribing in UK primary care clinics for patients with chronic obstructive pulmonary disease.[37] Prior studies have also suggested community antibiotic stewardship by pharmacists,[38] and prescribing or social norm feedback as part of continued GP education[35,39] or primary care accreditation schemes,[40] as means of reducing antimicrobial prescribing. Given the success of these initiatives in reducing antibiotic use in routine practice, coupled with low expected costs of implementation and GPs being easily accessible in a single hospital setting, there is every possibility to reduce antibiotic use.

Implications for research and practice

Given the increasing demands on emergency care, integrative care approaches are a plausible means of increasing capacity and caseload management, particularly given the non-urgent nature of many attendees to the ED. The results of this large-scale natural experiment showed that children seen by a GP in the ED waited less time, had fewer inpatient admissions, and lower costs, but experienced higher antibiotic prescribing than those treated by ED teams. However, further research incorporating causative study designs are required to determine causality between GP management and these outcomes.

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Ethical approval

Approval to conduct the study was granted by the Quality and Governance Team at Alder Hey Children's NHS Foundation Trust (reference number: 5511).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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Chapter 5 – Publication contribution statement

EDC, LN, DTR and MR devised the study. EDC, MR, BM and AC supervised the collection of data. LD, HA, SM, VO, KE, PJ, BM and SL helped collect the data. SL, FC, BM and DTR planned all statistical analyses, while SL and LN planned all economic analyses. SL performed all statistical and economic analyses, including data cleaning. SL wrote the first draft of the manuscript in conjunction with JR, EDC, LN, DTR and FC and revised and approved the final manuscript as submitted. All authors helped draft the manuscript and approved the final submitted version.

Chapter 6: The cost-effectiveness of point-of-care testing for febrile children attending the ED: An economic modelling-based evaluation

Abstract

Background Emergency departments (EDs) face many challenges in maintaining high-quality care in the face of steadily increasing public demand, and one key challenge is ensuring the appropriate use of antibiotics. Estimates suggest that between 20% and 50% of antimicrobial prescribing in paediatric emergency care may be clinically unnecessary, particularly so among those presenting with paediatric febrile illness. This overuse of antibiotics may not only impact children in the short term, but also result in longer-term increases in antimicrobial resistance and the sub-optimal use of scarce healthcare resources.

Methods A decision tree was constructed to model a hypothetical cohort of 831,000 febrile children attending paediatric EDs over a one-year period. The figure of 831,000 was chosen to reflect the estimated number of ED attendances by febrile children every year in the United Kingdom as reported by Hospital Episode Statistics (HES) data. The model primarily compared two strategies: (1) the existing standard of care, as based on clinical guidelines, primary and published data, and (2), the same care pathway with the addition of a POC test during triage. Care pathways with GP-led management included in each arm of the model were also included as secondary analyses, resulting in four care pathways in total. The model incorporated micro-

costed estimates of overall health service costs (triage, clinical, radiography, pathology, inpatient and antibiotics), antimicrobial prescribing rates, and patient satisfaction with care. Sub-group analyses accounted for the impact of patient heterogeneity, while one-way and probabilistic sensitivity analyses and scenario analyses modelled the impact of uncertainty on all outcomes under consideration.

Results In the base-case analysis, it was uncertain whether POC testing would be cost-effective relative to existing care, with an incremental cost-effectiveness ratio (ICER) of (-) £86.42 (95% CI -£978.08, £437.12) per antibiotic prescription avoided, and mean cost-savings per patient of £7.64 per child (95% CI £116.92 (cost saving), £38.24 (cost increase)). Both parental and healthcare provider utility increased significantly as a result of POC testing, with POC-testing reducing ED visit time by 34 minutes (95% CI -22 minutes, 190 minutes) for the average child. The cost-effectiveness of POC testing was significantly higher among infants aged <6 months, where POC testing was a strictly dominant strategy, with mean patient savings of £67.82 (95% CI £14.69, £450.31) per patient, an ICER of -£657.43 (95% CI, -£127.31, -£2,534.29), and a time saving of 66 minutes (95% CI -75 minutes, 359 minutes) . POC cost-effectiveness was most impacted by the ability to rule in/rule out bacterial causes of fever (minimum 26% reduction in avoidable antibiotic prescriptions required to remain cost-saving), adherence to POC test results (minimum 52% adherence to required remain cost-saving) and the cost of the POC test (maximum price of £17.50 required to remain cost-saving). Probabilistic sensitivity analysis suggested a 68.8% probability that POC testing would be dominant from a health economic perspective when used among all children with fever regardless of age

(willingness to pay per antibiotic prescription avoided of £0, in addition to a decrease in antimicrobial prescribing). When willingness to pay per antibiotic prescription avoided increased to £50, there was an 84.5% probability of cost-effectiveness among all children. Among those aged <6 months and >6 months respectively, there was a 97.9% and 66.2% probability of dominance over existing care.

Interpretation Based on a conservative set of assumptions, the results suggest that POC testing is likely to be more cost-effective than the current standard of care for the management of paediatric febrile illness, reducing healthcare costs, clinically unnecessary antibiotic use, and both HCP and parental satisfaction with care. However , this requires further examination if POC testing is to be used in children of all ages, as the value of POC testing was far greater for those aged <6 months. More research will be required to determine the true impact of improved POC tests on the management of paediatric febrile illness, while discussion around the willingness to pay for reductions in antimicrobial prescribing at a policy level, should also be considered before any firm conclusions are made. POC test costs, ability to rule in/rule out bacterial causes of fever and adherence to test results will be key factors in determining the real-world value of POC testing.

Background

EDs face many challenges in maintaining high-quality care in the face of steadily increasing public demand. One key challenge is ensuring the appropriate use of antibiotics, with estimates suggesting that between 20% (Denny, et al. 2019) (Leigh, Grant, et al. 2018) and 50% (Santander, et al. 2018) (Messina, et al. 2019) of

antimicrobial prescribing in paediatric emergency care may be clinically unnecessary, as observed in chapters three and five of this thesis. However, the mechanisms underlying antimicrobial prescribing in paediatric emergency care are complex and influenced by several factors. At the parent level these include parental requests (Mustafa, Wood, et al. 2014) (Huang, et al. 2007) (Nyquist, et al. 1998), anxiety (Crocetti, Moghbeli and Serwint 2001), and misconceptions about the appropriate applications and efficacy of antibiotics. While from a healthcare provider perspective, understanding of and commitment to the benefits of antimicrobial stewardship may also play a role.

Chapter three of this thesis demonstrated that diagnostic uncertainty is also a major contributor to antimicrobial prescribing (Leigh, Grant, et al. 2018) (Whaley, et al. 2013), and this is common during the management of paediatric febrile illness. While most children with fever will suffer from self-limiting viral illnesses, clinical presentations of those with bacterial or viral illnesses are often similar (Baraff 2000). Hence, while the use of antibiotics is clinically necessary in approximately 8% of febrile children (Leigh, Grant, et al. 2018), reflecting the underlying prevalence of bacterial infections seen within emergency care; up to 64% of febrile children are reported to receive antibiotics (van de Maat, et al. 2019). However, antibiotics are not a benign intervention, and unnecessary or inappropriate antibiotics can lead to both patient and community harms. These include the harms associated with adverse events (Tamma, Avdic and Li 2017) including *Clostridium difficile* infection (Owens, et al. 2008), treatment failure, and AMR (Maillard, et al. 2020); while offering limited or

no therapeutic benefit (Currie, et al. 2014). Evidence from the UK also suggests that febrile children who receive clinically unnecessary antibiotics can be expected to incur significant increases in scarce ED resource utilisation and subsequent treatment costs, equal to approximately £1,000 per child (Leigh, Grant, et al. 2018), or £2,500 in the case of infants, where the likelihood of serious bacterial infections is far greater (Irwin, Drew and Marshall 2015) (Gangoiti, et al. 2018) (Irwin, Grant and Williams 2017). However there are also opportunity costs of coping with diagnostic uncertainty, in that the use of inpatient beds, observation areas, nursing time, medicines, and diagnostic services by these children, a group who already account for considerable ED resource utilisation (Leigh, Grant, et al. 2018), may have produced a greater benefit if redirected to those with a greater clinical need.

In a time where fast, efficient, and personalised care has become increasingly demanded and important, POC tests, which have been both successful (Haldrup, et al. 2017) (Briel, et al. 2006) (André, et al. 2008), and well received (Cals and van Weert 2013) (Howick, Cals and Jones 2014) within primary care, may be one solution to achieving a more appropriate and measured use of antibiotics within EDs. Several readily available POC tests have shown promise in the diagnosis of a variety of infectious diseases, including those measuring capillary CRP (Mintegi 2018) (Roulliaud, et al. 2018) (Ivaska, et al. 2015), serum (Lee, et al. 2020) and whole blood procalcitonin (Shim, et al. 2019) (Shapiro, et al. 2018), and lactate (Goyal, et al. 2010). If they are capable of changing clinical practice, use of these diagnostic technologies may not only limit the emergence and global spread of antimicrobial resistant microorganisms, but also be resource and cost saving (Roulliaud, et al. 2018) (Leigh,

Grant, et al. 2018), increase patient, parental and HCP satisfaction (Leigh, Robinson, et al. 2020), and decrease waiting times in otherwise overcrowded EDs (Garvey, et al. 2019).

Most POC tests presently undergo clinical performance assessment, however very few studies include broader impact on operational, economic, and preference-based outcomes (Verbakel, Turner, et al. 2017). As such, the real-world value of POC testing in generalisable ED settings, beyond clinical trials, remains unknown. This chapter builds on the findings of the preceding chapters in aiming to explore the economic and social value of ED-based POC testing for childhood infections under multiple care pathway scenarios, including GP-led management as introduced in the previous chapter. The primary outcome of the chapter is to examine the cost per antibiotic prescription avoided when comparing usual care and a hypothetical POC testing scenario. Secondary outcomes include exploring which characteristics, including adherence to test results by HCPs, uptake of POC-testing, turnaround time, POC-test price and POC-test sensitivity; are most likely to affect economic impact, satisfaction with care, and anti-microbial prescribing rates. These together are likely to drive real-world use of POC-testing for the diagnosis of infectious diseases in the ED.

Materials & Methods

Decision tree structure

A decision tree model was constructed using Microsoft Excel (version 2019) to simulate a hypothetical cohort of otherwise well febrile children attending UK EDs.

High-risk groups including the immunosuppressed or those within oncology pathways experiencing febrile neutropenia were excluded from this model as they were under investigation in a separate work package as part of the PERFORM study, which is yet to be concluded. Aside from being studied elsewhere, reasons for non-inclusion centred around the different care pathways that these children would experience compared to the "average" otherwise well febrile child. In the case of febrile neutropenia, rates of inpatient admission, and isolation away from other children are far more likely than for those who are otherwise well. Therefore the value of POC-testing within these groups, is likely to differ significantly to those estimated here. We ran the model 831,000 times as this figure represents the estimated number of annual paediatric ED attendances in the UK, based on 2020 HES data (Hospital-Episode-Statistics 2020) and estimates the proportion of these attendances attributable to febrile illness (Zachariasse, Borensztajn, et al. 2020) (Van den Bruel and Thompson 2014) (Nijman, Jorgensen, et al. 2020). The base-case or primary analysis compared complete pathway costs, antimicrobial prescribing rates, and both healthcare provider and patient satisfaction of a hypothetical POC testing scenario, with the same outcomes under a scenario that replicated the current standard of care. The model time horizon was limited to the period of the initial ED admission and any subsequent inpatient stay that may follow (based on data provided in Chapter 3) (Leigh, Grant, et al. 2018). No follow up was included.

Outcomes

Primary outcomes were total health service expenditure and antimicrobial prescribing rates, and the associated incremental cost-effectiveness ratio (ICER), between the POCT scenario and the current standard of care, as shown in Equation (1). The ICER provides information on the additional cost per unit of additional benefit between a treatment option (POC testing) and the next best alternative (the current standard of care). Here, the ICER represented the additional cost per antibiotic prescription avoided, an outcome measure reported in several previous economic evaluations (Tillekeratne, et al. 2019) (Oppong, et al. 2018) (Takemura, et al. 2005). Being a UK-focused study, the economic perspective was a health services perspective; although below we also describe broader patient- and HCP-related preference outcomes.

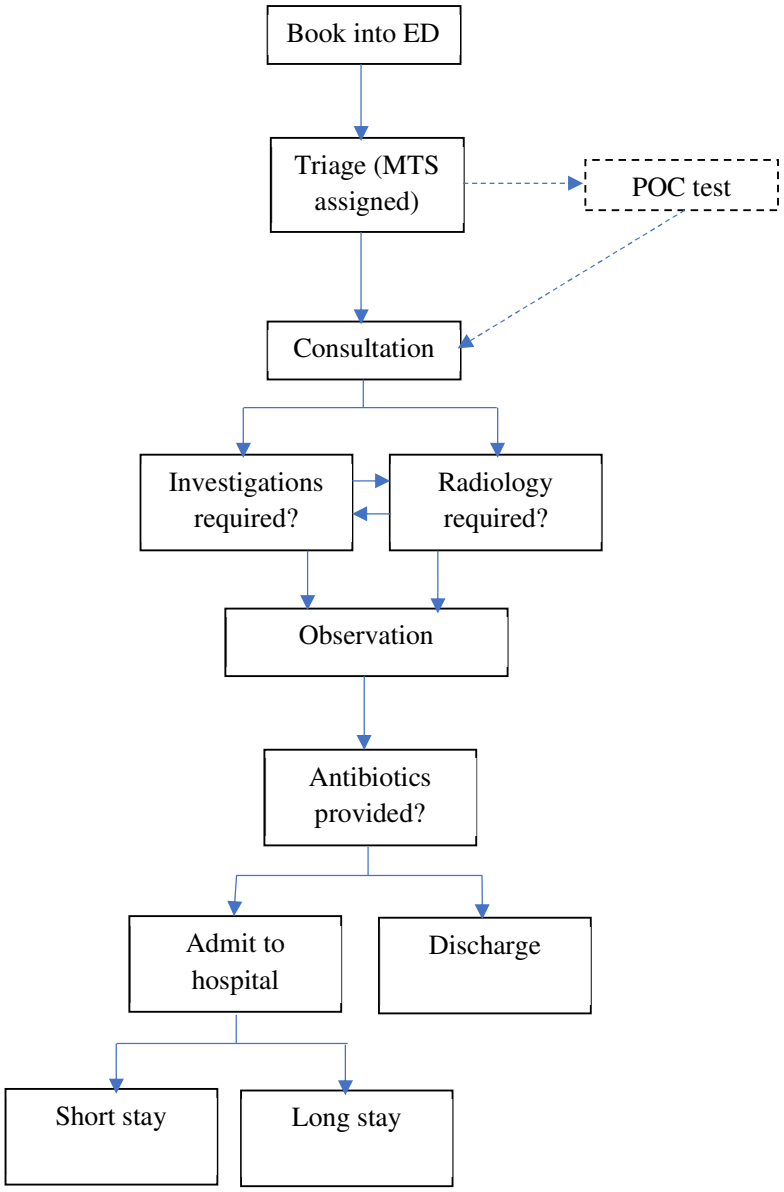
Secondary outcomes assessed operational and preference-based outcomes important in determining the overall value, and satisfaction with care, but not affecting health outcomes directly (Leigh, Robinson, et al. 2020) (Brazier, Dixon and Ratcliffe 2009). This included satisfaction with care from both a healthcare provider and parental perspective. Given the short-term acute emphasis of the model, AMR was not considered as an outcome.

Equation 1. $$ICER_X = \frac{Cost_{POC} - Cost_{CURRENT\ SOC}}{\%\ antibiotic\ free_{POC} - \%\ antibiotic\ free_{CURRENT\ SOC}}$$

Patient pathway (current standard of care)

A simplified version of the patient pathways underpinning the model, based on time-in-motion exercises and pathway mapping undertaken in Chapter 3, is provided in Figure 30. Based on current established paediatric febrile illness clinical practice patterns (Leigh, Grant, et al. 2018) (NICE 2017), the model assumed that after being booked into the ED, children were seen by a qualified ED nurse who conducted a triage evaluation, using the MTS (Zachariasse, et al. 2017). MTS assessments follow a flow chart based on the patient's reason for contacting the ED. The chart begins by identifying possible criteria indicating life-threatening conditions for the patient, and if none of these conditions are present, the nurse continues along the flow chart asking questions until the nurse assigns the patient an appropriate category. In the model children were triaged as green 'standard', yellow 'urgent', orange 'very urgent' or red 'immediate attention'. Due to similarity in clinical risk, outcomes and healthcare costs, as illustrated in Chapter 3 (Leigh, Grant, et al. 2018), the orange and red categories were combined into a single state within the model.

Figure 30: Pathway for the management of paediatric febrile illness in the ED



Following triage, children waited for a consultation with an ED clinician, at which point there was a chance that children may leave the ED while waiting to be seen by

clinical teams. Following consultation children received one or more of blood and urine tests, radiography, or observation and monitoring to rule in, or rule out causes of fever. Following this period children were either admitted as inpatients or discharged. Among those admitted, antibiotics may or may not be prescribed. The model accounted for infections of all aetiologies from viral to bacterial, trivial, and unknown, the relative frequency of each within the model were based on observational data reported in a previous chapter (Leigh, Grant, et al. 2018), in addition to previously unpublished observational data collected from 13,508 consecutive febrile children over a two-year period. These categories were used to determine where antimicrobial prescribing was clinically necessary.

Patient pathway (POCT)

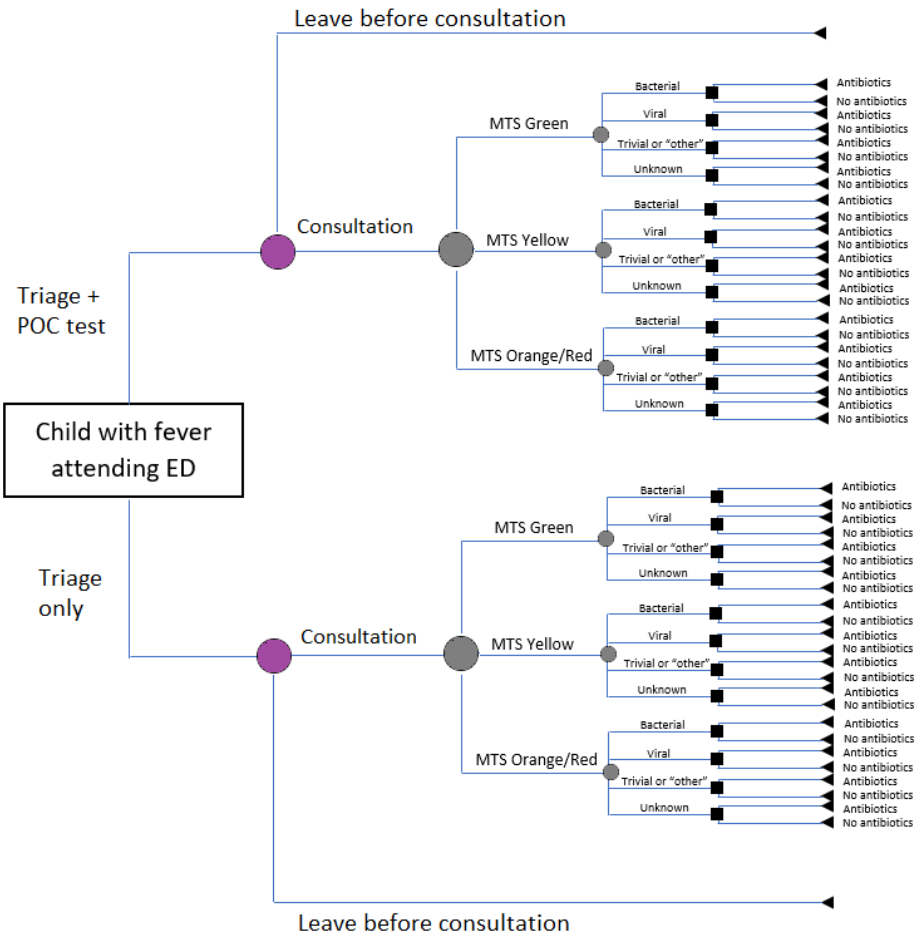
For those receiving POC testing, it was assumed the test was performed during triage. In the absence of published data regarding the likely sensitivity and specificity of any hypothetical POC test which may be used for the management of paediatric febrile illness, these values were imputed based on previous literature. The sensitivity of the POC test was assumed to be 90%, based on an average of the findings of chapters 3 (Leigh, Grant, et al. 2018) and 5 (Leigh, Mehta, et al. 2020), and a recent multi-country analysis of antimicrobial prescribing among 35,650 febrile children by Haagedoorn et al. (N. Hagedoorn, et al. 2020). In the absence of data concerning the expected specificity of the test, this was also estimated based on previously published literature. Chapter 3 of this thesis demonstrated that 32.1% of a cohort of 6,518 febrile children managed in the ED received antibiotics, of which 7.1% were retrospectively classified

as bacterial in nature. This resulted in a specificity of antimicrobial prescribing under existing care of 22.1%, similar to a 2021 ED-based study of children with URTIs which estimated that 22.4% of antibiotic prescriptions in the ED were clinically necessary (Sánchez, et al. 2021). A recent meta-analysis concerning the impact of CRP-POC testing on antimicrobial prescribing rates among children in emergency care (Verbakel, Lee, et al. 2019) demonstrated that POC testing reduced clinically unnecessary antimicrobial prescribing by 44%. The estimate provided in the meta-analysis was based on two randomised controlled trials including 1,710 children, which studied the impact of CRP POC tests which were also provided with guidance on interpreting the results of the tests, a practice which is common when providing diagnostic tests (Powell, et al. 2021) (Do, et al. 2019) (Lemiengre, et al. 2014). We combined the sources provided above, reducing potentially unavoidable antibiotic prescribing, which equalled 77.9% under existing care (Leigh, Grant, et al. 2018), by 44% (Verbakel, Lee, et al. 2019). This reduced the 'false positive' rate for antimicrobial prescribing to 43.6% under the POC testing scenario, giving a conservative estimated specificity of 56.4%.

Because the results of POC tests are not guaranteed to be adhered to, or to feature in decision making for some HCPs, for reasons including being too busy to use the test, to mistrust in the results (Pai, et al. 2015) or a lack of familiarity with the test (Quinn, Dixon and Meenan 2016), the effectiveness of a POC test in promoting reduced antimicrobial prescribing was reduced further. The model assumed that adherence and translation of the results of a POC test into practice was 86%, based on data from two recent RCTs (de Vos-Kerkhof, et al. 2015) (Lacroix, et al. 2014).

Additionally, it was assumed that the POC test took 8 minutes to perform, 33% longer than similar CRP-tests performed in adults (Hunter 2015) (HIQA 2019), to allow for the difficulties of performing assessments in children who may be in distress. Finally, it was assumed that the test took four minutes to return results, based on similar POC tests available at the time of completing the analysis (Abbott 2021). A pictorial demonstration of the model, including cost groupings, is provided in Figure 31.

Figure 31: Simplified flow through the model



Costs include triage time, urine investigations (and POC test if applicable)

Additional costs of consultation with clinician, and those associated with performing blood and radiography investigations

Additional costs of antibiotics (whether oral or IV) and those associated with both short and long stay inpatient admission

Model parameters

Epidemiology

All parameters utilised for the model, in addition to measures of uncertainty expressed in terms of plausible distributions, are provided in Table 31. The 831,000 children within the hypothetical model cohort were based on HES data collected in 2020 detailing the prevalence of paediatric ED attendances to NHS hospitals (4,681,214) (Hospital-Episode-Statistics 2020). The proportion of these attendances attributable to febrile illness was then estimated. There is considerable variability among published literature regarding the proportion of paediatric ED attendances that are a result of fever, with estimates ranging from 7.5% in a large EU multi-country study (Zachariasse, Borensztajn, et al. 2020) to 14% in a larger UK-based study (Van den Bruel and Thompson 2014), to 28% in a recent single-centre study based in the UK (Nijman, Jorgensen, et al. 2020). Given the uncertainty inherent to estimating this figure from heterogenous samples characterised by varying timeframes and inclusion criteria, a reciprocal variance weighted average of these estimates would have been the ideal means of smoothing these estimates. However, in two instances, based on observational data where the proportion of febrile children was imputed rather than reported, standard deviations were not available. In the absence of this information the mean of these estimates was used in the base case of the model. We therefore assumed that 17.75% of all paediatric ED attendances were associated with fever.

Clinical parameters, and triage

Data concerning the distribution of MTS classifications for different age groups, and the likely cause of fever among children (viral, bacterial, unknown and trivial/other), were obtained from previously unpublished data concerning the ED management of 13,508 consecutive febrile children at a single tertiary care provider in the Northwest of England, collected from July 2015 to July 2017. The likelihood of children leaving before being seen by a clinician post-triage, was obtained from a study of 6,518 febrile children details of which are provided in Chapter 3 (Leigh, Grant, et al. 2018).

Investigations, antibiotics & hospital admissions

The probability of receiving a blood culture, X-ray, or any urine investigation, including urinalysis and urine culture, was dependent on MTS classification and based on the findings of Chapter 3 (Leigh, Grant, et al. 2018). Following consultation and investigations, the likelihood and duration of both short and long stay hospital admissions was based on previously unpublished data concerning 13,508 consecutive febrile children collected from a single site in the Northwest of England between July 2015 and July 2017. This data stratified length of stay by a combination of both aetiology of fever and the age of the child, both of which have previously been shown to impact duration of both short and long stay inpatient admission (Leigh, Grant, et al. 2018) (Leigh, Mehta, et al. 2020). Finally, the likelihood of a child receiving antibiotics, whether oral or intravenous, was also dependent upon both the aetiology of fever and the age of the child and based on the findings of two studies, a European

study of 35,650 febrile children recruited from 12 children's hospitals in eight countries (N. Hagedoorn, et al. 2020), and a study of 6,518 febrile children in the UK, detailed in Chapter 3 of this thesis (Leigh, Grant, et al. 2018).

Given the previously reported relationship between patient age, the probability of SBIs, and both healthcare expenditure (Leigh, Grant, et al. 2018) (Leigh, Mehta, et al. 2020), and use of antimicrobials (Leigh, Grant, et al. 2018), in addition to parental anxiety related to febrile illness (Leigh, Robinson, et al. 2020) (Gunduz, et al. 2016), several key model parameters were estimated for three distinct groups: (1) those of all ages, (2) those aged <6 months, and (3) those aged > 6 months. This enabled the model to account for various sources of heterogeneity. Parameter value estimates, and measures of uncertainty, for all variables included in the model are listed within Table 31.

Table 31: Epidemiology and clinical parameters used within the model

Variable	Value	Distribution	Reference
Annual ED attendances among children aged 0-16 years	4,681,214	N/A*	Hospital Episode Statistics 2020
Percentage of ED attendances among children related to febrile illness	17.75%	N/A*	Mean of three studies, (Zachariasse, Borensztajn, et al. 2020) (Van den Bruel and Thompson 2014) (Nijman, Jorgensen, et al. 2020)

Annual ED attendances among children aged 0-16 years related to febrile illness	831,000	N/A*	Calculation (4,681,214 (paediatric ED attendances) * 17.75% (proportion related to fever)
TRIAGE & CONSULTATION			
MTS triage classification *(%)* *(All children)*			Unpublished data collected from 13,508 febrile children (Leigh, Grant, et al. 2018)
Green	77.9	Beta (10529, 2979)	
Yellow	8.2	Beta (1109, 12399)	
Orange/Red	13.9	N/A[#]	
MTS triage classification *(%)* *(Children aged <6 months)*			
Green	59.5	Beta (357, 243)	
Yellow	15.6	Beta (81, 519)	
Orange/Red	24.9	N/A[#]	
MTS triage classification *(%)* *(Children aged >6 months)*			
Green	79.1	Beta (10173, 2684)	
Yellow	8.0	Beta (1028, 11829)	
Orange/Red	12.9	N/A[#]	
Leave before consultation (%)			
MTS Green	4.8	Beta (148, 2943)	
MTS Yellow	0.8	Beta (5, 588)	
MTS Orange/Red	0.4	Beta (11, 2623)	
RADIOGRAPHY & INVESTIGATIONS			
Blood culture (%) *(All children)*			(Leigh, Grant, et al. 2018)
MTS Green	1.6	Beta (49, 3042)	
MTS Yellow	7.6	Beta (45, 547)	
MTS Orange/Red	5.8	Beta (153, 2481)	
X-ray (%)			
MTS Green	5.8	Beta (179, 2912)	
MTS Yellow	11.1	Beta (66, 526)	
MTS Orange/Red	15.1	Beta (398, 2236)	
Urine Sample (%)			
MTS Green	16.2	Beta (502, 2589)	
MTS Yellow	23.5	Beta (139, 453)	
MTS Orange/Red	21.3	Beta (562, 2072)	
Aetiology of fever (%)			

Bacterial	16.8	Beta (934,4485)	Unpublished data collected from 13,508 febrile children
Viral	24	Beta (1360 ,4059)	
Trivial	10.6	Beta (574, 4845)	
Unknown	48.6	N/A[#]	
Antimicrobial prescribing (%) ***(All children)***			
Bacterial	93.6	Beta (7386, 503)	Haagedorn et al. 2021
Viral	6.9	Beta (1418, 18965)	
Trivial	10.8	Beta (44, 363)	
Unknown	45.2	Beta (2348, 2852)	
Antimicrobial prescribing (%) ***(Children aged <6 months)***			
Bacterial	91.0	Beta (63,6)	(Leigh, et al. 2018)
Viral	13.4	Beta (9,61)	
Trivial	34.3	Beta (15,28)	
Unknown	31.4	Beta (61,133)	
Antimicrobial prescribing (%) ***(Children aged >6 months)***			
Bacterial	92	Beta (944, 82)	
Viral	5.9	Beta (62, 989)	
Trivial	8.6	Beta (56, 592)	
Unknown	46.1	Beta (1329, 1554)	
INPATIENT ADMISSION (DAYS)			
All children			
Bacterial (receives antibiotics)	1.84	Gamma (0.26, 7.24)	
Bacterial (no antibiotics)	1.24	Gamma (0.26, 4.84)	
Viral (receives antibiotics)	3.04	Gamma (0.84, 3.59)	
Viral (no antibiotics)	0.33	Gamma (0.09, 3.53)	
Trivial (receives antibiotics)	1.44	Gamma (0.45, 3.18)	
Trivial (no antibiotics)	0.58	Gamma (0.18, 3.19)	
Unknown (receives antibiotics)	0.21	Gamma (0.09, 2.33)	
Unknown (no antibiotics)	0.13	Gamma (0.13, 1)	
Children aged < 6 months			
Bacterial (receives antibiotics)	4.21	Gamma (0.3, 14.05)	

Bacterial (no antibiotics)	3.65	Gamma (0.27, 13.35)	(Leigh, Grant, et al. 2018)
Viral (receives antibiotics)	4.28	Gamma (1.92, 2.23)	
Viral (no antibiotics)	0.71	Gamma (0.16, 4.51)	
Trivial (receives antibiotics)	0.06	Gamma (100, 0)	
Trivial (no antibiotics)	0.19	Gamma (0.33, 0.57)	
Unknown (receives antibiotics)	1.37	Gamma (0.45, 3.04)	
Unknown (no antibiotics)	0.22	Gamma (0.07, 3.06)	
Children aged > 6 months			
Bacterial (receives antibiotics)	1.54	Gamma (0.35, 4.42)	
Bacterial (no antibiotics)	1.02	Gamma (0.4, 2.54)	
Viral (receives antibiotics)	2.71	Gamma (0.68, 3.99)	
Viral (no antibiotics)	0.29	Gamma (0.09, 3.24)	
Trivial (receives antibiotics)	1.67	Gamma (10.56, 3)	
Trivial (no antibiotics)	0.62	Gamma (0.19, 3.25)	
Unknown (receives antibiotics)	0.18	Gamma (0.08, 2.14)	
Unknown (no antibiotics)	0.13	Gamma (0.18, 0.74)	

POC TEST CHARACTERISTICS

Reduction in antibiotics from POC testing (%).	44	Beta (10.84, 8.52)**	(Verbakel, Lee, et al. 2019)
Adherence to POC test results (%)	86	Beta (188, 31)	(de Vos-Kerkhof, et al. 2015) (van de Maat, et al. 2019)
Time until obtaining POC test results (minutes)	4	Uniform (1, 10)##	Abbott, 2021
Time to perform POC test (minutes)	8	Uniform##	(Hunter 2015) (HIQA 2019)

** Distribution not utilised as this is a 'scene setter' and estimate of epidemiology. The aim of the model is not to analyse budget impact but rather to compare management scenarios therein. This figure would only act as a linear multiplier for any findings of the model*
 # Estimate obtained from remainder of other distributions when subtracted from one, in order to ensure proportions did not exceed one.
*** Distribution fitted from patient-level data provided in meta-analysis*
Assumed distribution due to absence of data

Health service cost and utility parameters

The model was calibrated from an NHS perspective, including all costs incurred within the entire treatment episode following initial presentation to the ED. A list of all unit costs used for the model are provided in Table 32. All costs are provided in 2019/2020 prices (GB, £) and inflated to 2019/2020 prices when based on previously published

estimates. Given the short time frame of the analysis, chosen to reflect the time children were in the ED and for any subsequent inpatient admission, costs were not discounted. Costing was performed by adapting an existing time-based TDABC approach, including the costs of nursing, clinical and healthcare assistant time, ancillary investigations, radiography, inpatient stay, and other consumables utilised within the ED. Hourly salaries for healthcare personnel were provided by the costing department at the Trust where the study was sponsored. Costs for non-time driven activities, including laboratory-based investigations, were obtained from NHS reference costs 2019/20 (NHS-Improvement 2019).

Antibiotics were assigned unit costs from the British National Formulary (BNF 2020). In the case of antibiotics being provided we assumed that detailed antibiotic prescribing was in line with the recommendations provided within NICE CG160 (NICE 2017). Health service costs incurred during both short and long-stay inpatient admission were obtained from NHS reference costs 2019/20 (NHS-Improvement 2019). In doing so, the tariff HRG PW20C (paediatric fever of unknown origin, CC score = 0) was multiplied by the expected number of inpatient days.

Finally, the cost of POC testing was assumed in the base case to be £10, based on a similar analysis of POC testing (Hughes, et al. 2016), while costs of implementing a change in practice, including training costs, and any hardware required for cleaning, maintenance or recalibration were not considered.

Utilities associated with febrile illness care pathways were calculated based on a recent stated preference study utilising a discrete choice experiment design, detailed in Chapter 4 of this thesis (Leigh, Robinson, et al. 2020). Utilities were included from

the perspective of both parents and healthcare providers and analysed separately, providing a holistic assessment of overall satisfaction with care processes from both perspectives. The model applied utility reductions for every one-minute increase in total time in the ED, for when invasive and potentially painful investigations (including venous blood sampling) were required, and when clinically unnecessary antibiotics were prescribed (defined as receiving antibiotics in the case of viral, inflammatory, or trivial infections in the absence of identified bacterial pathogens). The findings also report on the total amount of time children are expected to spend in the ED under all care scenarios under examination within the chapter, and highlighting any changes which may be attributable to the addition of POC-testing.

A complete list of utility estimates incorporated into the decision analytic framework are provided in Table 33. Because the absolute values of the utility scores are marginal part-worth utility increases or decreases relative to a specific alternative scenario and considered under a *ceteris paribus* scenario, the resulting combined utility scores for each management scenario have no practical meaning or interpretation (Hauber, et al. 2016) (de-Bekker Grob 2009). Therefore, utilities were expressed as relative changes in the POC arm of the model vs. the existing care arm. Enabling a percentage difference which can be interpreted relative to the alternative management pathway.

Table 32: Cost parameters for the economic model

Variable	Cost	Distribution	Reference
Investigations			
Urinalysis	£8.00	Fixed	NHS Reference Costs 2018/2019
Urine culture	£8.00	Fixed	NHS Reference Costs 2018/2019
X-ray	£46.00	Fixed	NHS Reference Costs 2018/2019
Blood Culture	£35.00	Fixed	NHS Reference Costs 2018/2019
Staff time (per minute)			
FY1/FY2	£0.40	Fixed	Hospital Finance Department*
ST1-3	£0.43	Fixed	Hospital Finance Department*
APNP	£0.46	Fixed	Hospital Finance Department*
Registrar	£0.65	Fixed	Hospital Finance Department*
Consultant	£1.27	Fixed	Hospital Finance Department*
Cost per inpatient day	£571	Fixed	NHS Reference Costs 2018/2019
Antibiotics	£54.48	Fixed	(BNF 2020)
POC test	£9.85	Uniform, £5 (min), £15 (max)	(Hughes, et al. 2016)

**Costs were inflated to 2019/2020 costs using the consumer price index.*

BNF, British National Formulary; FY1/FY2, Foundation Year 1 and 2; ST1-3, Specialist training years 1 to 3; APNP, Advanced paediatric nurse practitioner; POC, Point of Care.

Table 33: Utility parameters for the economic model

	Parents		HCPs	
	Value	Distribution	Value	Distribution
HCP treating child				
Trainee doctor	-0.244	Normal (-0.244, 0.076)	-0.204	Normal (-0.204, 0.046)
Nurse Practitioner	-0.135	Normal (-0.135, 0.077)	0.081	Normal (0.081, 0.02)
Consultant (reference group)	0.379	Normal (0.379, 0.124)	0.032	Normal (0.032, 0.05)
Likelihood of receiving antibiotics				
Low (reference group)	0.143	Normal (0.143, 0.231)	0.729	Normal (0.729, 0.103)
Medium	0.031	Normal (0.031, 0.278)	-0.111	Normal (-0.111, 0.02)
High	-0.174	Normal (-0.174, 0.189)	-0.618	Normal (-0.618, 0.201)
Moderate pain from investigations (relative to low)	-0.462	Normal (-0.462, 0.05)	-0.439	Normal (-0.439, 0.03)
Receive POC test during triage (relative to no)	0.627	Normal (0.627, 0.048)	0.723	Normal (0.723, 0.105)
Total time spent in the ED (per hour)	-0.608	Normal (-0.608, 0.058)	-0.679	Normal (-0.679, 0.07)
Out-of-pocket cost to parents (per £1)	-0.036	Normal (-0.036, 0.01)	-0.051	Normal (-0.051, 0.001)

**All distributions fitted based on observed variability in utility estimates for each parameter, collected during chapter 4 of this thesis.*

Sensitivity analyses

In addition to the base-case analysis, the impact of varying model parameter values was explored deterministically. That is, where one or more key parameters were varied based on changing the value of that parameter, while holding all other parameters constant at the base-case level. Where possible upper and lower limits for varying parameter values were informed by existing literature. For parameters where there was

insufficient literature to provide a plausible range of varying parameter values which may reflect wider population averages, these were varied using a mean +/- X% approach.

The varying of model parameter values reflected the uncertainty inherent to estimating both the costs and outcomes of existing care processes for febrile illness, and those concerning the likely impact of POC testing among children with febrile illness in the ED. POC-specific sensitivity analyses included: (1) a higher or lower POC test cost, (2) higher or lower reductions in antimicrobial prescribing from POC testing, which may be attributed to learning effects over time (Bikker, et al. 2020), differences in uptake among ED staff (Huddy, et al. 2016), or the possibility of a varying ability to rule in or rule out different pathogens in the case of panel tests, (3) differing adherence to POC test results, which may result from varying abilities to interpret results, as seen in previous studies (Verbakel, Lee, et al. 2019) (4) the ability of POC testing to reduce radiography and investigations (Andreeva and Melbye 2014), and (5) the potential for differences in the amount of time to perform the POC test with a child, particularly if they are anxious, scared or uncooperative (Lerwick 2016).

Finally, the model also explored the scenario of including GP-led management within the ED for non-urgent children, as discussed within the previous chapter (Leigh, Mehta, et al. 2020), and how POC testing may affect this increasingly popular care pathway (Kmietowicz 2014) (RCEM 2014) (Smith, et al. 2018) (Leigh, Mehta, et al. 2020). The reason for this decision was to understand not just the impact of POC-testing in the 'average' ED, but also in those which have followed, or are in the process of implementing recommendations from the royal college of emergency medicine in

embedding primary care within EDs. Assumptions regarding the impact of GP-led management are provided in Table 34 and based on findings from two previous UK-based GP-in-ED evaluations (Smith, et al. 2018), including Chapter 5 of this thesis (Leigh, Mehta, et al. 2020).

Table 34: Assumptions for GP-POC model

Variable	Value	Distribution	Reference
Proportion of MTS Green patients managed by GP	64.2%	Beta (8404, 4695)	(Leigh, Mehta, et al. 2020) (Smith, et al. 2018)
Antimicrobial prescribing rate via GP-management of MTS Green children	15.2%	Beta (1269, 7135)	(Leigh, Mehta, et al. 2020)
Antimicrobial prescribing rate via ED-management of MTS Green children	10.8%	Beta (507, 4187)	(Leigh, Mehta, et al. 2020)
Reduction in inpatient admission following GP-led management	82.5%	Beta (82.5, 17.5)	(Leigh, Mehta, et al. 2020) (Smith, et al. 2018)

** All distributions fitted from raw data provided in previous chapters*

Threshold analyses were conducted to determine the parameter value at which recommendations would change, with the results presented in the form of an adapted tornado diagram (Briggs, Sculpher and Claxton 2006). We also performed Monte Carlo probabilistic sensitivity analysis (PSA), consistent with best practice guidelines in stipulating distributions and characterising uncertainty (A. Briggs 2005) (Briggs,

Weinstein, et al. 2012), to determine the robustness of the model conclusions, converting discrete model inputs into distributions based on published literature and measures of uncertainty. All distributions utilised were, where possible, fitted distributions based on variability in outcomes of interest observed in their respective studies. For binomial parameters, beta distributions were employed, characterised using the 'alpha = successes, beta = failures' model. For continuous parameters gamma distributions were used, with alphas calculated as mean^2 / standard error^2 and beta equal to standard error^2 / mean as detailed elsewhere (Briggs, Sculpher and Claxton 2006). A uniform distribution was utilised for assessing the impact of uncertainty with regards to the cost of POC testing, in the absence of sufficient evidence to inform a credible distribution, ranging from £5 (NICE 2016) to £15 (NICE 2017).

Finally, for utilities, normal distributions were used which were fitted based on the variability (mean and standard deviation) demonstrated within the preference data for each parameter, collected during chapter 4 (Leigh, Robinson, et al. 2020). As the utility estimates for the parameters included in the model, which included both parental and HCP perspectives, varied from -0.61 to 0.63, and displayed symmetrical distributions, a normal distribution fitted the data well, whereas the usual choices of gamma or lognormal would have been unsuccessful due to bounding at zero, therefore not allowing the random generation of both positive and negative plausible utility values.

The PSA included 10,000 simulations and was performed using recommended procedures (Briggs, Weinstein and Fenwick 2012). Finally, all confidence intervals

were generated using the percentile method (Henderson 2005) (Walters and Campbell 2004).

Results

Base-case vs. POC scenario

The estimated cost of managing ED visits for paediatric febrile illness was £351.52 per child (95% CI, £184.06, £783.22) under the existing care scenario, reducing slightly, to £343.88 per child (95% CI, £162.97, £777.76) in the POC scenario, a saving of £7.64 per child (95% CI £116.92 (cost saving), £38.24 (cost increase)). In the absence of POC testing, 38% (95% CI, 35%, 39.4%) of children were expected to receive antibiotics, reducing to 29% (95% CI, 22%, 34.3%) following the introduction of POC testing.

Taking reductions in both healthcare expenditure and antimicrobial prescribing into account, the ICER (the cost per antibiotic prescription avoided) of moving from the current standard of care to POC testing, for all children presenting to the ED with fever was -£86.42 (95% CI, -£978.08, £437.12), suggesting that, in the base-case, a management strategy of POC testing may be dominant over the current standard of care, but with a confidence interval crossing zero, the uncertainty inherent to this estimation suggests that it cannot be guaranteed.

POC testing also provided additional utility/satisfaction with care over the existing care scenario, with both healthcare provider and parental utility increased by 6.2% (95% CI, -8.9%, 26.5%) and 5.2% (95% CI, -9.1%, 26.4%) respectively, while time

in the ED was reduced by 34 minutes (95% CI -22 minutes, 190 minutes). Using the utility coefficients calculated within Chapter four of this thesis, this 6.2% improvement in utility from POC-testing was valued at £41.11 by parents, suggesting that parents would hypothetically be willing to pay this to experience the total improvement in care resulting from the implementation of POC-testing.

GP-led management vs. GP-led management + POC

We additionally explored whether POC-testing may add additional value to febrile illness care pathways with GP- led management included, as recommended by the RCGP and explored during chapter 5 of this thesis (Leigh, Mehta, et al. 2020). The findings presented in Table 35 demonstrate that the lowest cost management strategy for managing paediatric febrile illness in the ED would be GP-led management + POC-testing, which reduced the cost per episode down to £227.68 (95% CI, £147.77, £581.34), compared to £233.46 (95% CI, £161.17, £586.33) under GP-led care without POC testing, £351.52 per child (95% CI, £184.06, £783.22) under the current standard of care in the absence of POC testing, and £343.88 per child (95% CI, £162.97, £777.76) under the current standard of care with the addition of POC testing.

Table 35: Economic, clinical, preference-based, and operational outcomes of POC-testing + GP-management vs existing care + GP-management, for the management of paediatric febrile illness

	GP-led management	GP-led management + POC	Difference
All children			
Cost (Per patient)	£233.46 (95% CI, £161.17, £586.33)	£227.68 (95% CI, £147.77, £581.34)	-£5.78 (95% CI, -£64.60, £38.13)
Antibiotics (%)	41% (95% CI 39%, 44%)	29% (95% CI (27.2%, 29.9%)	-12% (95% CI, -11.3%, -15.2%)
Utility (Parents)	N/A*		7.2%
Utility (HCPs)			6.5%

**Absolute utility values associated with care pathways have no meaningful interpretation as they are by definition comparative.*

In the absence of POC testing, 41% (95% CI, 39%, 44%) of children managed by GPs in the ED were expected to receive antibiotics, reducing to 29% (95% CI, 27.2%, 29.9%) following the introduction of POC testing.

Taking reductions in both healthcare expenditure and antimicrobial prescribing into account, the ICER (the cost per antibiotic prescription avoided) of moving from GP-led management to GP-led management + POC testing, for all children presenting to the ED with fever was -£48.16 (95% CI, -£201.25, £194.68), suggesting that, in the base-case, a management strategy of GP-led management + POC testing may be dominant over GP-led management alone, but again, with a confidence interval crossing zero, it cannot be guaranteed.

Sub-group analyses

The value of POC testing varied with respect to the child's age, and for children aged >6 months was reduced considerably when compared to infants aged <6 months. Among children aged >6 months, the POC testing scenario was estimated to save approximately £4.25 per child (95% CI, -£47.63 (cost increase), £111.81 (cost decrease)), a 30 minute reduction (95% CI -14 minutes, 105 minutes) and a 9% (95% CI, 6.8%, 15.2%) reduction in antimicrobial prescribing, from 38% to 29% as demonstrated within Table 36. Using the utility coefficients elicited in Chapter four, this change in care resulting from the implementation of POC-testing was valued at £37.93 among parents, therefore denoting their hypothetical willingness-to-pay for such changes.

Conversely, for infants aged <6 months, POC testing was estimated to result in a reduction in healthcare expenditure of £67.82 per child (95% CI, £14.69, £450.31), from £789.15 under the existing care scenario, to £721.33 with POC testing in place; in addition to a 10% (95% CI, 8.1%, 18.6%) reduction in antimicrobial prescribing, from 42% to 32%, and a 66 minutes (95% CI -75 minutes, 359 minutes) reduction in time waiting in the ED. This change in care resulting from the implementation of POC-testing was valued at £63.99 among parents, therefore denoting their hypothetical willingness-to-pay for such changes.

This resulted in ICERs of -£657.43 (95% CI, -£127.31, -£2,534.29) and -£48.95 (95% CI, -£605.94, £441.33) for children aged <6 months and >6 months respectively. This

suggests that POC testing is likely to be a dominant strategy from a health economic perspective, for children aged <6 months, but remains of largely uncertain value for children aged >6 months.

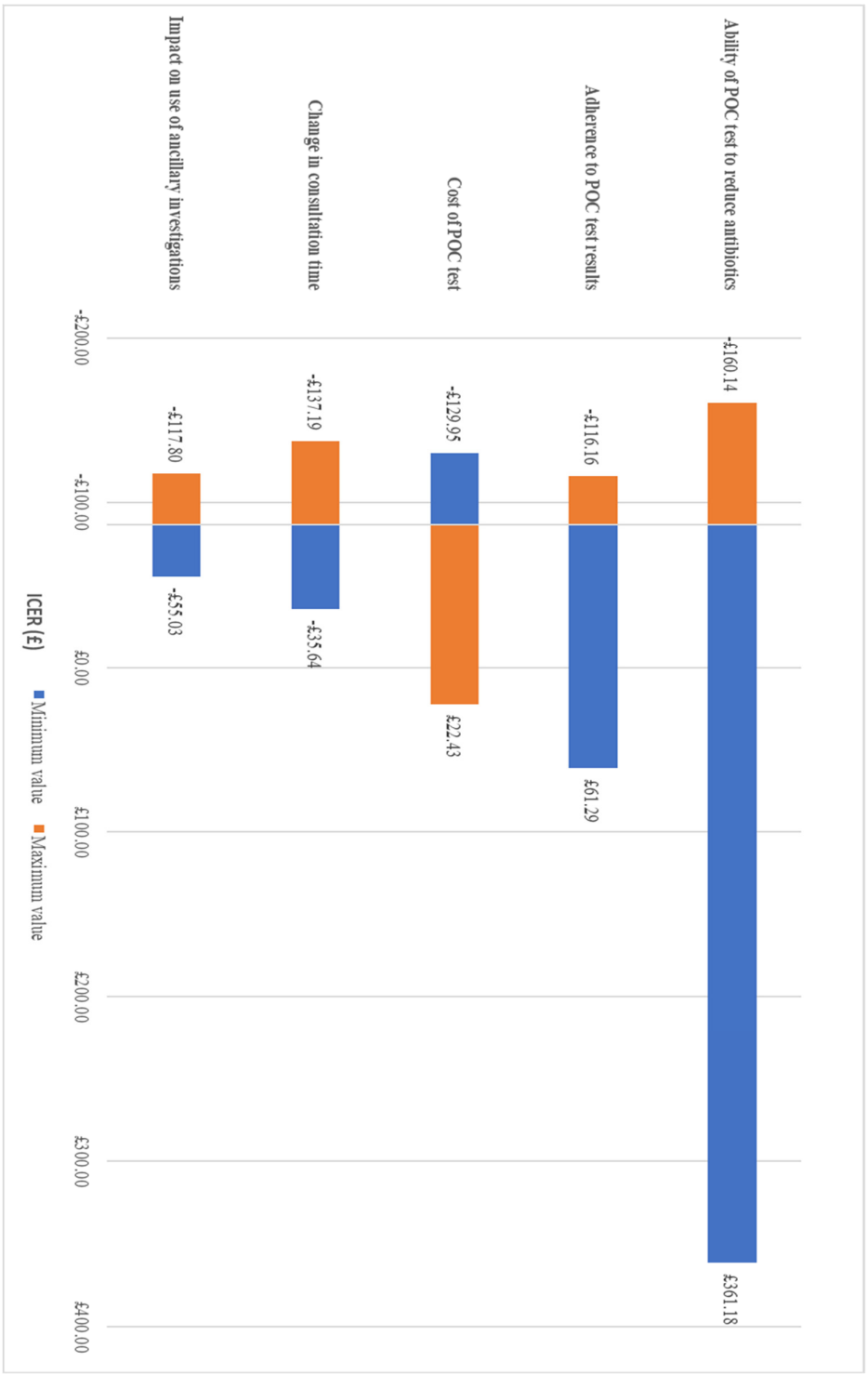
Table 36: Economic, clinical, preference-based, and operational outcomes of POC-testing vs existing care for the management of paediatric febrile illness

	Current SOC	POCT	Difference
All children			
Cost per child	£351.52 (95% CI, £224.06, £788.22)	£343.88 (95% CI, £142.97, £717.76)	£7.64 (95% CI, £116.92, -£38.24)
Antibiotics (%)	38% (95% CI, 35%, 39.4%)	29% (95% CI, 22%, 34.3%)	9% (95% CI, 6.9%, 15.5%)
Utility (Parents)	N/A		+5.20% (95% CI, -9.1%, 26.4%)
Utility (HCPs)			+6.20% (95% CI, -8.9%, 26.5%)
Children aged <6 months			
Cost per child	£789.15 (95% CI, £307, £2,884.25)	£721.33 (95% CI, £188, £2,679.72)	£67.82 (95% CI, £14.69, £450.31)
Antibiotics (%)	42% (95% CI, 39.7%, 45.2%)	32% (95% CI, 23.7%, 34.6%)	10% (95% CI, 8.1%, 18.6%)
Utility (Parents)	N/A		+8.40% (95% CI, -9.9%, 26.1%)
Utility (HCPs)			+8.50% (95% CI, -9.8%, 26.5%)
Children aged >6 months			
Cost per child	£311.66 (95% CI, £64.17, £1102.36)	£307.41 (95% CI, £59.06, £1090.95)	£4.25 (95% CI, -£111.81, £47.63)
Antibiotics (%)	38% (95% CI, 34.9%, 39.3%)	29% (95% CI, 22.2%, 31.7%)	9% (95% CI, 6.8%, 15.2%)
Utility (Parents)	N/A		+5.50% (95% CI, -8.8%, 26.2%)
Utility (HCPs)			+5.70% (95% CI, -8.6%, 26.5%)

Sensitivity analyses

Results of the primary sensitivity analyses are provided in an adapted tornado diagram (Figure 32).

Figure 32: Tornado diagram demonstrating impact of parameter assumptions on cost-effectiveness of POC-testing



The ability of a POC test to reduce clinically unnecessary prescribing of antimicrobials impacted cost-effectiveness substantially, as did adherence to the results of POC testing, resulting in changes in practice. The cost of a POC test also somewhat affected POC cost-effectiveness, however the ability of a POC test to impact the usage of subsequent investigations including x-ray, blood and urine culture, and the ability of a POC test to reduce consultation time, had no significant impact on the cost-effectiveness of POC testing. The threshold values, at which point POC testing was no longer cost-saving, were 26% (reduction in avoidable antibiotics), £17.50 (cost of POC test), and 52% (adherence to POC test results). Additional sensitivity analyses which utilise alternative parameter values from published sources, in addition to a range of values between published estimates, are provided in Table 37. This table demonstrates the robustness of the primary outcome of the chapter, the ICER representing the cost per antibiotic prescription avoided, to changes in these parameters.

Table 37: One-way sensitivity analyses

Analysis	Parameter description	ICER
Base Case		-£86.42
Threshold analyses		
Cost of test		
	Cost of test = £5[1]	-£129.95
	Cost of test = £10[2]	-£86.42
	Cost of test = £15[3]	-£31.99
	Cost of test = £17.50	**£0**
	Cost of test = £20	£22.43
Ability of test to reduce antimicrobial prescribing		
	Reduction in avoidable antibiotics = 10%[4]	£361.18
	Reduction in avoidable antibiotics = 19%[5]	£86.80
	Reduction in avoidable antibiotics = 26%	**£0**
	Reduction in avoidable antibiotics = 44%[5]	-£86.42
	Reduction in avoidable antibiotics = 50%[6]	-£111.52
Adherence to results of test, and correct translation into practice		
	Adhering to results of test = 40%	£61.29
	Adhering to results of test = 52%	**£0.00**
	Adhering to results of test = 78%[7]	-£64.82
	Adhering to results of test = 85%[8]	-£86.42
	Adhering to results of test = 100%	-£116.16
Scenario analyses		
Change in consultation time from using POC test		
	Increase in consultation time = 50%	-£35.64
	Increase in consultation time = 25%	-£66.11
	No change in consultation time	**-£86.42**
	Reduction in consultation time = 25%	-£116.88
	Reduction in consultation time = 50%	-£137.19
Change in senior-level consultations (registrar & consultant)		
	Increase in senior consultation = 50%	-£75.74
	Increase in senior consultation = 20%	-£82.14
	No change in senior consultation	**-£86.42**
	Reduction in senior consultation = 20%	-£90.69
	Reduction in senior consultation = 50%	-£97.09
Reduction in use of ancillary investigations		
	Increase in ancillary investigations = 40%	-£55.03
	Reduction in ancillary investigations = 20%	-£73.86
	No change in ancillary investigations	**-£86.42**
	Reduction in ancillary investigations = 20%[12]	-£98.97

	Reduction in ancillary investigations = 40%[13]	-£117.80
Antimicrobial prescribing rate among non-bacterial causes of fever		
	Non-bacterial antibiotic prescribing = 6.96%[9]	**-£86.42**
	Non-bacterial antibiotic prescribing = 15%	-£201.45
	Non-bacterial antibiotic prescribing = 25%	-£322.92
	Non-bacterial antibiotic prescribing = 30%[10]	-£373.91
	Non-bacterial antibiotic prescribing = 40%[11]	-£461.09

1. (NICE 2016)
2. (Hunter 2015)
3. (NICE 2017)
4. (Diederichsen, et al. 2000)
5. (Verbakel, Lee, et al. 2019)
6. (Peters, et al. 2013)
7. (Althaus, et al. 2019)
8. (de Vos-Kerkhof, et al. 2015) (van de Maat, et al. 2019)
9. (N. Hagedoorn, et al. 2020)
10. (Denny, et al. 2019) (Milani, et al. 2019)
11. (Kiel, et al. 2020)
12. (Andreeva and Melbye 2014)
13. (Groeneveld, et al. 2019)

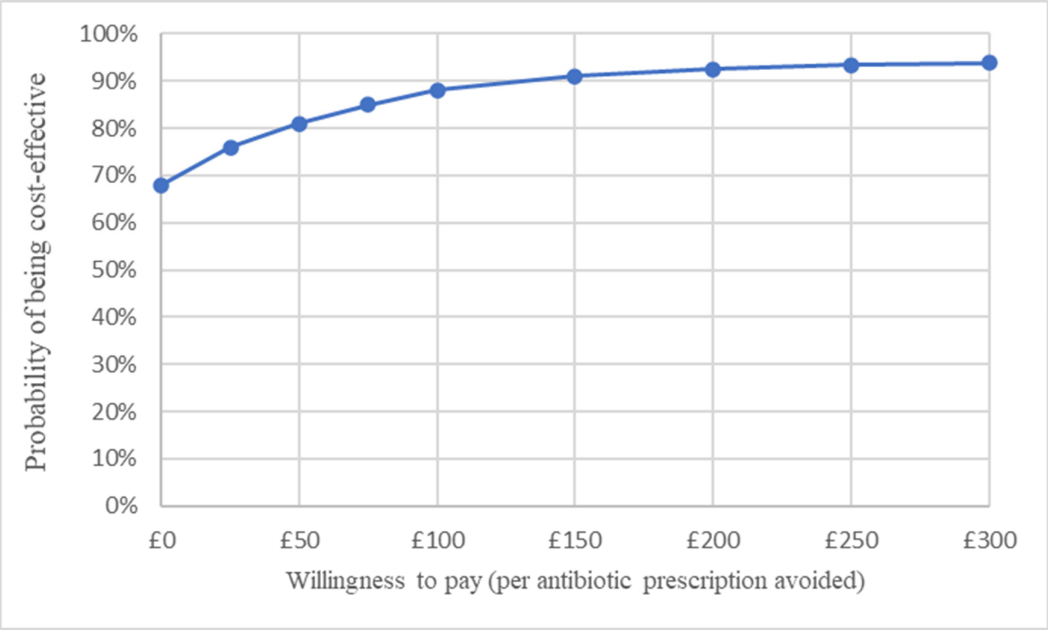
Probabilistic sensitivity analysis

The cost-effectiveness acceptability curve (CEAC) demonstrated in Figure 33 shows the probability of POC testing being cost-effective at varying WTP thresholds. The cost-effectiveness acceptability curve (CEAC) is a graph summarising the impact of uncertainty on the result of an economic evaluation, frequently expressed as an ICER (incremental cost-effectiveness ratio) in relation to possible values of the cost-effectiveness threshold. The graph plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective, when compared to a comparator, in this case existing care, at that threshold on the vertical axis (Fenwick, O'Brien and Briggs 2004). At a WTP of £0 per antibiotic prescription avoided, POC testing had a 68.8% probability of being cost-effective compared to existing care for all children regardless of age. When increasing the WTP to £50 this increased to 84.5%, and at a WTP of £300, was 94.5%. Among children

aged <6 months, and >6 months, there was a 97.9% and 66.2% probability respectively of POC testing being more cost-effective than existing care.

Figure 33: Cost-effectiveness acceptability curve for POC testing

A: Children of all ages



Discussion

Summary of principal findings

This study compared costs, antimicrobial prescribing rates, satisfaction with care, and the cost-effectiveness of an approximation of the existing standard of care vs. the use of POC testing, for the ED-management of paediatric febrile illness. The findings demonstrated that under a set of assumptions informed wholly by existing literature

(cost £9.85; antibiotic reduction 44%; adherence to results 86%, time to perform test 8 minutes), POC testing is estimated to both more successful and less expensive than the current standard of care in minimising clinically unnecessary antimicrobial prescribing. The addition of GP-led management for non-urgent cases (i.e. GP-management + POC-testing), as recommended in previous studies (Smith, et al. 2018) (Leigh, Mehta, et al. 2020), reduced both health service costs and antimicrobial prescribing further still. At the population-level, considering all estimated annual ED presentations for paediatric febrile illness in the UK, the estimated health-service savings from switching to POC-testing equalled £6.3m per year, if this was achieved in every ED within the UK. Sensitivity analysis demonstrated that the factors most influential in shaping the cost-effectiveness of POC-testing were, in descending order, the cost of the test, ability to rule in/ rule out bacterial infections, the underlying level of non-bacterial antimicrobial prescribing, and adherence to POC test results. Under base-case assumptions, the cost of POC testing could increase to £17.50 per test and remain cost-neutral. Using probabilistic Monte Carlo simulation POC testing had a 68% probability of being a dominant strategy compared to usual care (lower costs and reduced antimicrobial prescribing). Sub-group analysis highlighted that the value of POC testing varied significantly with patient age, with those aged <6 months receiving the greatest benefit, and a 97.9% probability of both cost savings and reductions in antimicrobial prescribing.

Strengths & limitations

Our study had several strengths. Consistent methods were employed to construct a highly detailed and generalizable model, with data inputs from various sources,

including meta-analyses, RCTs, prospective observational studies and clinical audits. This ensured representative and accurate depictions of the care pathways experienced by febrile children, under both experimental and real-world conditions. Additionally, detailed observational and audit data for more than 20,000 febrile children (Leigh, Grant, et al. 2018) (Leigh, Mehta, et al. 2020) enabled informative sub-group analyses, while uncertainty in multiple input parameters was accounted for by Monte Carlo PSA, ensuring the conclusions reached were assessed for robustness and any sensitivities identified.

Several potential limitations of the analysis should also be considered. Firstly, we utilised epidemiological estimates and care pathway structures specific to the UK. As a result, these may not be completely representative of, or generalisable to other countries. Additionally, while it is thought that most UK clinicians will follow the NICE CG160 guidelines for children under 5 years (NICE 2017), which largely informed our model structure, it can be expected that there is diversity in the testing and management strategies employed to meet specific patient needs. These may be impacted by several factors including parental pressures or anxiety, clinical acumen or previous experience. Furthermore, there is currently no guideline for children aged >5 years, who represent a significant proportion of our modelled patient population, and of those observed in previous chapters where patient-level data was collected. These limitations may also limit generalisability of our findings. However, we believe that the use of PSA allowed and accounted for such variability, enabling sufficient pathway variation based on a multitude of literary estimates, and the uncertainty inherent to each, for all parameters. Next, due to the myriad of bacterial pathogens

observed in routine practice, and the resulting wide array of targeted single and combination antimicrobial therapies, it was difficult to accurately define antimicrobial resource use within the model. Similarly, the future costs of AMR were not included. As such, our estimates should be considered conservative. Moreover, in the absence of sufficient published information regarding the probable characteristics of our hypothetical POC test, our model relied on estimating plausible values for sensitivity and specificity, based on previously published real-world evidence. The studies identified instead focused on the combined ability of a test to reduce potentially avoidable antimicrobial prescribing as observed in previous investigative studies (Verbakel, Lee, et al. 2019) and systematic reviews (Martínez-González, et al. 2020). As a result, the estimate of a 44% reduction in avoidable antibiotics was assumed to be the result of a test sensitivity of 90%, and a specificity of 56.4%. While a sensitivity of 90% appears high, it is important to note that this was derived from previous studies, including chapters within this thesis (Leigh, Grant, et al. 2018) (Leigh, Mehta, et al. 2020) and a recently published multi-country analysis of antimicrobial prescribing among 35,650 febrile children (Hagedoorn, et al. 2020). These studies collectively demonstrated a very high rate of antimicrobial prescribing (87% - 93.6%) among those with bacterial causes of fever; a result of most bacterial aetiologies being identified rather than missed by clinical teams in the ED. Therefore, the model assumed it unlikely that POC testing would result in significant changes in the ability of HCPs to identify children with bacterial causes of fever and initiate antibiotics.

Consequently, while our model is informed by published evidence, the interpretation of what a POC test must look like, from an implementation perspective, is not as clear

as it could have been if further data concerning the sensitivity and specificity of similar tests in paediatric populations were available.

Another limitation of this chapter concerns the likelihood that the cost data used to estimate the economic costs of POC and non-POC pathways were likely over-estimated. We used net-ingredient costs provided by the NHS, these costs represent baseline costs prior to the negotiation of discounts by Trusts. While this data detailing the precise costs of the consumables and diagnostics used were not publicly available, this remains a limitation as any discounts achieved effectively lower the price of managing the condition

Additionally, use of the consumer price index to inflate healthcare cost parameters provided from earlier published studies, may also represent a limitation. While the use of the CPI to provide a net present value is common within academic research and health research more specifically, other alternatives may have been used which more accurately reflect how inflation impacts prices within healthcare settings. Use of the Hospital and Community Health Services (HCHS) Index may have led to a more accurate representation of present day costs, and therefore without a comparison of how each compared against one another, this should be considered as a limitation. A final limitation is that staffing and consumable cost data used in the model were average costs. In the real-world, it may be expected that sites use staff of different grades and salaries to perform similar tasks and negotiate different costs for consumables, implying an inevitable variation in how cost-effective the different strategies would be for different sites. The same argument can also be made for a differential value of POC testing in centres of excellence, including specialist

paediatric hospitals vs. non-specialist hospitals. This distinction, and the possibility for a differential value of POC testing was also not examined within the model.

Interpretation considering other evidence

Clinically unnecessary antimicrobial prescribing, use of broad-spectrum antibiotics, and continuing antibiotics for longer than necessary are key drivers of AMR, which can make even procedures such as minor surgery and routine operations high-risk, increasing the duration of illness and in some cases leading to premature mortality (UK.government 2016). A review on AMR published in 2016 found that 700,000 people die each year due to resistant infections and it is estimated that by 2050 the world will face an additional 10 million deaths due to AMR infections at a cost of $100 trillion to the global economy (WHO 2019). As such, the finding that POC testing, based on a conservative set of assumptions, could reduce antimicrobial prescribing by 10% among those aged <6 months is an important one, and in keeping with previous literature (Leigh, Grant, et al. 2018). A prior observational study concerning the management of febrile children showed significant increases in antimicrobial prescribing among those with viral causes of fever aged 0-3 (20.8%), and 3-6 months (10%) (Leigh, Grant, et al. 2018). This may be due to a higher prevalence of invasive bacterial infections, bacteraemia and bacterial meningitis in this group, or the manifestation of uncertainty and perceived clinical risk in a known high-risk group (Elkon-Tamir, et al. 2017). Irrespective of the mechanisms underpinning antimicrobial prescribing rates among infants, POC testing demonstrated a clear added value to existing management approaches, despite the fact

that our assumptions regarding current clinically unnecessary antimicrobial prescribing rates under existing care were highly conservative, especially when compared to alternative published estimates (Harnden, et al. 2007) (Wilkes, et al. 2009). This value is also likely to be significant among smaller and more clinically distinct subpopulations, including children who are immunocompromised or under oncology pathways and experiencing febrile neutropenia. Therefore, despite being studied elsewhere as part of our research consortia, a key limitation of this chapter, and this thesis more generally, is a lack of data concerning high priority groups, and the value of POC-testing within these groups, where the likelihood of inpatient hospitalisation is far greater. Further research, including research currently being conducted as part of the PERFORM work package, should, in time, elucidate the true value of POC-testing in these groups.

The ability of POC testing to reduce overcrowding is also of significance. Overcrowding is a key safety concern not just for those attending the ED with febrile illness, but for all conditions, which can have a significant impact on the timeliness and quality of care in the ED. Prolonged waiting times and overcrowding have been associated with substantial delays in the administration of antibiotics (Institute of Medicine Committee on the Future of Emergency Care in the U.S. Health System 2006) and pain medication (Pines and Hollander 2008), and increases in mortality (Guttmann, et al. 2011) (Sprivulis, et al. 2006). The problem is exacerbated further in cases of sepsis, where the initiation of goal-directed therapy within the first three to six hours of presentation to the ED has been found to improve mortality rates by 16% (Dellinger, et al. 2013) (Rivers, et al. 2001). Our finding that POC testing led to a

mean 53-minute reduction in ED short-stay (within the waiting room), therefore signifies significant additional benefits from POC testing which could not be captured in the model. This benefit may be increased in larger hospitals where the distance between ED departments, and laboratories or radiography departments, are further apart, and where transit times for both testing and the processing of results add to the duration of patient stay. A recent study from chapter 3 of this thesis, highlighted that those receiving clinically unnecessary antibiotics experience a 54 hour increase in hospital visit duration (Leigh, Grant, et al. 2018), therefore any therapeutic advances which can minimise this time will likely not only benefit patient and carer satisfaction, but also free up these resources for children with a greater clinical need.

Implementation strategies are likely to be highly influential in the long-term cost-effectiveness and sustainability of POC testing. The use of POC testing can place additional responsibilities on those with already heavy workloads, such as ED nurses, the staff members who are most likely to perform POC testing. Publications from the Netherlands and the United States report that the number of tests ED providers seek to make decisions is limited, and therefore the appetite for such technologies may presently be below what is required to make POC testing a success (Storrow, Zhou and Gaddis 2008) (van de Wijngaart, Scherrenburg and van den Broek 2014). Other barriers to implementation include concerns around diagnostic accuracy (Turner, Van den Bruel and Jones 2016), and the perceived impact of testing on clinical acumen over time.

Additionally, the sensitivity of POC cost-effectiveness to changes in POC test adherence is an important consideration which requires further research, and it is

important to state the paucity of data relating to adherence to POC testing. We found two studies, both experimental in nature, which suggested an adherence rate to POC testing, and similar disruptive technologies, of between 85% (de Vos-Kerkhof, et al. 2015) and 93% (van de Maat, et al. 2019). It is likely that the experimental nature of these studies was in part a contributor to higher rates of adherence, and it may be expected that real-world use may be lower, where changing practice patterns can be difficult. Fear of confrontation with parents who expect a certain type of care, which may include antimicrobials, is likely a factor limiting the success of POC testing, something observed for malaria POC testing in Tanzania (Chandler, et al. 2014), and CRP POC testing in Europe (Yardley, et al. 2013). As clinicians may feel directly pressurised by parents to prescribe antibiotics (Rousounidis, Papaevangelou, et al. 2011), fear of conflict may negate the benefit of testing and still lead to the untargeted use of antibiotics.

Interpretation

Based on a conservative set of assumptions, the results suggest that POC testing is likely to be more cost-effective than the current standard of care for the management of paediatric febrile illness, reducing healthcare costs, clinically unnecessary antibiotic use, and ED waiting times. The value of POC-testing in reducing clinically unnecessary interventions among those with paediatric febrile illness can also be supplemented further with GP-in-ED care models. Finally, the value of POC testing was far greater for those aged <6 months where both diagnostic uncertainty and the likelihood of serious bacterial infections are greatest. More research will be required

to determine the true impact of improved POC tests on the management of paediatric febrile illness. RCTs with adjunct cost-effectiveness analyses are likely to play a significant role in this process, including the PRONTO trial examining the use of procalcitonin POC testing among adults with fever in the ED (PRONTO 2019) Based on the findings of this and those of the preceding chapters it is highly likely that POC test costs, ability to rule in/rule out bacterial causes of fever and adherence to test results will be key factors in determining the real-world value of POC testing.

Chapter 6 - Summary

The aim of this chapter was to follow up on the findings of all preceding chapters, to provide a comprehensive analysis of the potential value of POC testing for febrile illness in emergency departments. Chapter 3 demonstrated a clear economic value of improved febrile diagnostics; with a focus on a small cohort whose data were collected in the Northwest of England in 2012. This chapter was supplemented by the findings of chapter 4, which reported for the first time, on what matters to both parents and healthcare providers alike when managing paediatric febrile illness, using an iterative approach. The findings of this chapter highlighted that both parents and HCPs feel strongly about the avoidance of pain and achieving a faster diagnosis in the context of managing paediatric febrile illness; additionally, both HCPs and parents cared strongly about reducing ED visit times. Chapter 5 explored the previous themes of economic efficiency and both HCP and parental satisfaction further. Given that an increasing number of ED attendances are non-urgent, including in the case of paediatric febrile illness, they may be amenable to treatment in primary care. While there is limited

evidence, previously reported benefits of introducing GPs in EDs for managing non-urgent cases, include reduced waiting times (Goodman, Gordon and Martin 2014) (Smith, et al. 2018), and reductions in invasive examinations (Khangura, Flodgren and Perera 2012). The findings of chapter 5, a large-scale natural experiment, suggested that co-locating a GP in paediatric EDs is likely to reduce waiting times, inpatient admissions, and treatment costs significantly. In the context of chapters three and four, this represents a potential improvement, with both economic costs and satisfaction with care improving as waiting times, and the use of invasive and often clinically unnecessary invasive investigations decreases. However, the results of chapter 5 demonstrated that this benefit is likely to come at a cost, an increase in antibiotic prescribing. In the context of paediatric febrile illness, this may be problematic given the already high rates of antimicrobial prescribing experienced within a group which will predominantly be experiencing self-limiting and often clinically benign viral illnesses. While the results of chapter 5 demonstrated that the inclusion of GPs in EDs can be expected to reduce the pressure on frontline services, thereby freeing resources to treat more urgent cases, they would likely need to be accompanied by diagnostic improvements which can reduce reliance on antimicrobials among GP-treated patients. The final empirical chapter of this thesis, chapter 6 explored this theme further, building upon the findings of all the previous chapters combined. Using economic evaluation techniques, the economic costs, parental & HCP satisfaction with care, and antimicrobial prescribing rates associated with several care pathways for the ED-management of paediatric febrile illness were explored. Based on a conservative set of assumptions, the results of this concluding chapter suggested that POC testing is likely to be more cost-effective than the current standard of care for the management

of paediatric febrile illness, reducing healthcare costs, clinically unnecessary antibiotic use, in addition to improving satisfaction with care from both a HCP and parental perspective. Satisfaction with care, economic and clinical outcomes were most favourable when POC testing was used in addition to GP-led management. However further examination of the role and value of POC testing is required if POC testing is to be used in children of all ages. As has been observed in all preceding chapters, it is clear that the value inherent to POC testing, and the improvements that can be made upon existing care processes, differ among children of different ages. The value of POC testing was far greater for those aged <6 months, and for children of all ages, was sensitive to changes in POC test costs, ability to rule in/rule out bacterial causes of fever and adherence to test results. Based on the findings of this chapter, these will be key factors in determining the real-world value of POC testing and further research is required to provide greater certainty around population estimates for each of these parameters.

Chapter 7: Discussion

Introduction

This chapter begins by summarising the key findings in relation to objectives 1-5 of this thesis. Following this is a description of the contribution of the studies to the existing literature, which extends beyond the initial objectives in two main areas; our understanding of the economic and patient/parent-centric impact of paediatric febrile illness generally; and specific methodological advances achieved throughout the collective works of this thesis. There is then a discussion of the strengths and limitations of the overall approach taken to determining the socioeconomic value of diagnostic innovations for managing paediatric febrile illness in the ED, in addition to a critique of the collective study designs used. Finally, policy implications arising from the chapter findings are discussed, concluding with recommendations for future research.

Key findings with reference to objectives

Objective 1: Among children presenting to the ED with febrile illness, what is the economic impact of investigating and managing the condition? How much healthcare resource is dedicated to this and what role does diagnostic uncertainty play in this process?

Chapters 2 and 3 addressed the first objective of this thesis, with an in-depth literature review identifying a clear gap in existing knowledge, pertaining to the economic

implications of managing paediatric febrile illness in ED-settings. This led to an empirical examination of existing care pathways and resource use among an observational and representative cohort of 6,518 febrile children recruited over a one-year period.

Chapter 2 demonstrated that there is a paucity of evidence regarding the true financial impact of paediatric febrile illness in EDs, with stark variability in reported resource utilisation and subsequent healthcare resource impact. Just six studies were identified, the majority of which originating in the United States over a period of 25 years, raising concerns regarding generalisability within publicly funded modern healthcare systems. There were several limitations of all studies included and quality appraisal suggested consistent concerns with respect to study design and reporting. Furthermore, all the studies identified examined clinically distinct vignettes of children of varying presenting complaints, with one common underlying symptom, fever. No study had previously assessed the economic impact of managing paediatric febrile illness from a complete ED perspective, including children with varying aetiologies of fever and reasons for ED attendance.

Following on from the evidence gap identified within chapter 2, the third chapter reported on the largest prospective observational study to date, assessing the economic implications of managing paediatric febrile illness in those aged 0-16 years, in an ED setting. In a full cohort analysis employing a TDABC approach, the mean cost per febrile child was ~£223, however this was impacted by several key patient and healthcare provider characteristics. Infants aged 0-6 months (particularly those aged

0-3 months), those triaged as MTS yellow or above, and those managed by lesser experienced clinicians (FY1 and FY2), required significantly greater resources in the ED. This was primarily a result of increases in observation time for patients and increases in short stay admissions, the latter particularly prominent among those receiving antibiotics.

Diagnostic uncertainty increases resource use, drives clinically unnecessary antibiotic use, and places significant strains on ED capacity.

A total of 32.4% of febrile children in the study were prescribed antibiotics, of whom 7.1% were retrospectively diagnosed with bacterial aetiologies of fever. Children receiving antibiotics with retrospectively proven viral aetiologies of fever spent an additional 53.9 hours as inpatients (57.1 vs. 3.2 hours) compared to children with viral aetiologies of fever who were not prescribed antibiotics. This was accompanied by a 9.9-fold increase in management costs for those who received potentially avoidable antibiotics (£1,392.30 vs. £140.10), reaching a maximum of £2,843 vs. ~£480 in those aged <3 months. As a result, any advances in diagnostic capabilities including molecular diagnostics, protein biomarkers and POC tests, which may increase confidence to withhold antibiotics or discharge febrile children home from the ED earlier, could yield potentially significant economic and efficiency gains.

Objective 2: What are the factors which drive resource use when investigating febrile illness, are these patient or healthcare professional-related?

Chapter 2 addressed the second objective of this thesis initially, with a literature review finding highly variable costs of managing paediatric febrile illness in ED-settings. These were however confounded by systemic differences in study methodologies and analysis of clinically distinct groups, making comparison and synthesis of studies difficult. Chapter 3 filled this evidence gap, using GLM among a broad and representative group of febrile children, of varying diagnoses and ages, to identify factors associated with increased ED resource use for the management of paediatric febrile illness, the findings were:

There are several factors driving resource use, which are centred on proxies for increased risks of serious bacterial infection.

Those aged 0-3 months exhibited a mean treatment cost over 6-fold higher than the least costly group, those aged 3-6 years. Use of blood cultures, urine samples, inpatient admission rates, and inpatient length of stay, were all significantly increased for those aged 0-3 months, versus all other age groups. Increasing clinical severity, as proxied by increasing MTS classifications, also resulted in significant cost increases compared to children triaged as green. The presence of a NICE NG51 respiratory rate red flag also increased costs by 72.1%. Other factors associated with increased resource use included treatment by FY1/FY2 doctors, (3.19-fold, relative to the consultant reference group); however, when considering only non-urgent children, triaged as green using the MTS, FY1/FY2 doctors exhibited a 7.98-fold increase in costs of

management. Children seen by FY1/FY2 doctors had the highest rates of inpatient admission, ancillary investigations, and referring children to other specialties.

Following Monte Carlo simulation and re-running our GLM on 100 bootstrapped datasets, children triaged as MTS yellow or above, those prompting a NICE NG51 respiratory rate red flag, those treated by an FY1/FY2 doctor, and those aged 0-3 months, 3-6 months or 10-16 years respectively, were statistically significant predictors of increased healthcare costs in 100% of simulations.

Objective 3: What matters to parents when their children are being investigated for fever in the ED, and similarly, what matters to the healthcare professionals providing care?

Chapter 4 addressed this objective, with an in-depth iterative approach based on a literature review, followed by focus-groups and a coin-ranking exercise and culminating in a discrete-choice experiment conducted among both parents and HCPs. The findings were:

Reducing waiting times is important particularly as it is associated with anxiety

Reducing waiting times was highlighted as an area for considerable improvement when attending the ED with a febrile child. This was observed in the focus-groups, coin-ranking exercise and DCE, respectively. Reducing waiting times was the single most important characteristic of care and parents were willing to spend £16.89 (95% CI £8.30 - £26.88) of their own money if it meant reducing waiting times by just one-

hour. The reason for this centred around increasing levels of anxiety while waiting, and feelings of being forgotten while their child is unknowingly deteriorating in the ED. Parents also expressed almost unanimous discomfort with what they believed to be 'bothering' or interrupting staff if they perceived their time waiting in the ED to be excessive, or if they believed they had been forgotten. Specifically, there was a strong aversion to being seen to be ignoring the reality that other, perhaps more acutely ill children may need treatment first; an issue which is likely to be common given the often non-urgent nature of attendances related to paediatric febrile illness.

Minimising pain and discomfort from diagnostic tests (including venous blood sampling) is very important to both parents and HCPs

Pain and discomfort associated with investigations was associated with significant dissatisfaction among both parents and HCPs, remaining important across all sub-groups analysed. The importance of reducing pain where possible was clear from the initial focus-groups and coin-ranking exercise and then re-iterated during the DCE. Parents viewed pain from investigations as a necessary sacrifice to gain diagnostic information to better manage their child's condition, but would much rather have this information via less traumatic means to their child if possible. This was particularly true among parents of younger children who could not articulate to their children that venous blood sampling for example, was necessary to help the child start to feel better. Despite waiting times being very important, parents were willing to wait an additional 45.6 minutes (95% CI (-)19.3mins – 60.4mins) to avoid incurring pain from investigations, suggesting an indicative window for POC-tests to return results within,

provided that they can also minimise the discomfort experienced by the child, by moving from venous to capillary blood sampling for example.

While clinicians with more experience are preferred, clinical experience does not really matter, unless parents genuinely believe something is seriously wrong, or if their child is very young, and cannot communicate their symptoms effectively.

Preferences regarding who treated febrile children were highly variable. In general, parents preferred their children being overseen by more experienced clinicians (consultants and registrars were specifically mentioned), and parents reported being willing to wait an extra 24.1 minutes (95% CI (-) 15.9mins – 46.9mins) to see a consultant, if the alternative was being seen by a doctor in postgraduate training. This time increased if parents believed the condition was something more serious than 'just a fever', or if their child was younger. Although the DCE confirmed the importance of clinical experience, the preceding focus-groups uncovered several benefits of febrile children being managed by doctors in postgraduate training. These included reduced waiting times, knowledge being 'fresher in their minds', and a perceived increased likelihood of being able to communicate more effectively with younger children. Parents were also acutely aware of the reality that lesser experienced clinicians would likely consult those with greater experience if they had any concerns, suggesting that while consultants and registrars were preferable, *'just being seen by anyone'* was likely to result in satisfaction with care.

Lower SES groups displayed no preferences either for or against the use of antibiotics, higher SES groups however, preferred not to receive them; a preference shared with HCPs, who demonstrated a strong preference for reducing antibiotic use among febrile children where possible.

A moderate (20%) to high (33%) probability of receiving antibiotics reduced satisfaction with care considerably among those educated to University level or higher, or among those with a household income of >£40,000 per year. Among those educated to college level or less however, or with a household income of <£40,000 per year, receiving antibiotics did not affect utility satisfaction with care. Factors driving this finding included awareness of the side-effects of antibiotics, with parents citing Public Health England's 'keep antibiotics working' jingle. Similarly, all HCP subgroups preferred not to prescribe antibiotics, particularly doctors. HCPs also reported a willingness to extend patient waiting times by 39.9 minutes (95% CI (-) 30.9mins – 79.5mins) if it reduced the likelihood of prescribing antibiotics to febrile children.

POC-testing (or other forms of rapid diagnostics for use among those with febrile illness) are likely to improve patient and parent/carer satisfaction, and HCP confidence with care significantly.

Providing a POC test during triage, which may provide diagnostic information earlier, was associated with significantly increased satisfaction with care both among parents and HCPs. This desire for what are perceived as the primary benefits of POC testing, namely, reducing the time waiting for clinical updates about the severity of the

condition causing febrile illness, was the most valued aspect of care during the coin-ranking exercise, with almost 80% more coins than any other attribute. The reason for this, expressed during the focus-groups, was a desire to receive information quicker than is currently possible, and assuage any concerns that parents may have, making the remainder of any wait in the ED less stressful as the thought of deterioration or serious illness would at least in part be negated.

Similarly, HCPs expressed utility in a POC-test being available during triage, valuing it more than reducing antibiotic use, as this reduced the diagnostic uncertainty faced by clinicians making decisions about the febrile child in real-time. When combining the possible secondary benefits of POC testing, including reducing the need for venous blood sampling, and reduced waiting times, children, carers and HCPs are all likely to benefit considerably from developments in infectious disease diagnostics. These are expected to provide increased confidence in timely and evidence-based decision making.

Objective 4: Given that many children with febrile illness are classed as non-urgent, what impact would GP-led emergency care have on patient, operational and economic outcomes?

The findings of chapter 4 demonstrated that waiting times were a major cause of dis-satisfaction with existing febrile illness care pathways. Chapter 5 built upon these findings in the pursuit of answering objective 4; could GP-led care provide economic, operational, or clinical benefits for those with non-urgent conditions, such as febrile

illness in the ED. Using a prospective cohort-control study of all non-urgent presentations to a single ED over a two-year period, the findings were:

GP-led care for non-urgent attendances reduced waiting times & increased the number of children being seen and discharged within the 4-hour target.

The median duration of stay in the ED was 39min (IQR 16–108) for the GP group compared with 165 min (IQR 104–222) for the ED group. Management by the onsite GP was associated with significantly reduced odds of breaching the Department of Health and Social care four-hour waiting standard (OR 0.10; 95% CI 0.084 to 0.125) with 98.6% of children in the GP group and 88.4% in the ED group discharged or admitted within four hours.

GP-led care also reduced short and long-stay inpatient admission among non-urgent ED presentations.

The odds of being admitted were significantly lower for children managed by the onsite GP (OR 0.16; (95% CI 0.13 to 0.20); $p<0.001$). Short stay admissions of <6 hours were reduced by 84.7%, 24-hour admissions by 86.5% and admissions exceeding 1 day by 78.7% for those seen by the GP. Children in all age groups and diagnostic groups were statistically significantly more likely to be admitted to hospital if managed by ED clinical teams.

Healthcare and societal costs of children managed by onsite GPs were significantly lower than those managed by ED teams.

The mean cost of treatment episodes for the GP group was significantly lower than those managed by ED clinicians £115.24 (95% CI £20.50 - £351.67), compared to £141.16 (95% CI £11.78 - £539.94). Both groups recorded similar costs attributable to medications prescribing, and investigations, while costs associated with staff salaries (receptionist, nurse, doctor) were much higher in the GP group. The primary difference in costs came from inpatient admission costs, which were significantly lower in the GP-group, owing to a 75.3% reduction in median inpatient duration (0.22 days vs. 0.89 days). Societal costs were also increased 2.38-fold (£46.87 vs. £18.53) in the ED group.

Antimicrobial prescribing was also increased among those managed by onsite GPs

Rates of antibiotic prescribing were 15.1% in the GP group, compared to 10.8% in the ED group, (OR 1.42; (95% CI 1.27 - 1.58)). Compared to children managed by ED teams, children managed by the GP who were seen and discharged within one-hour had an odds ratio of 3.32 (95% CI 2.2-5.0) for being prescribed antibiotics. Specifically considering children managed by the GP group with fever at presentation, a 10.4% increase in antibiotic prescribing was observed (27.1% vs. 16.7%). Taking into account the possibility for differential presentations and aetiologies of fever, which may have explained the significant differences in approaches to antimicrobial prescribing, approximately 89.9% of children with fever receiving antibiotics in the

GP group, compared to 75.9% in the ED group, did not have bacterial aetiology, suggesting these antibiotics may have been avoidable.

Could GP-led care be a solution for the increasing number of febrile presentations in EDs, and potentially decrease waiting times and improve clinical, operational, and economic outcomes?

Given the increasing demands on emergency care, integrative care approaches are a plausible means to increase capacity and manage caseload, particularly given the non-urgent nature of many attendees. The results of this large-scale natural experiment showed that children seen by the GP in the ED waited less time, had fewer inpatient admissions, and lower costs, but experienced higher antibiotic prescribing than those treated by ED teams. Probabilistic sensitivity analysis suggested an 86% probability that GP-led care would result in a saving of at least £30 per patient, while similarly, there was a 98.3% probability that treatment by GPs in the ED would increase antibiotic prescribing by at least 3%.

Advances in diagnostic technologies such as rapid POC testing may play a role in reducing unnecessary antibiotic prescribing, therefore, if used in conjunction with GP-led care, may improve outcomes while assuaging concerns related to increased antimicrobial prescribing. It is uncertain however, whether this would prove to be a cost-effective venture.

Objective 5: Could POC-testing for infectious diseases be a cost-effective use of scarce NHS resources when managing paediatric febrile illness in the ED? What are the factors that influence cost-effectiveness most?

Chapter 6 addressed this objective, with a health-economic model, based around a cost-consequence (and nested cost-effectiveness) methodology, attempting to demonstrate the likely overarching health service impact of POC-testing for paediatric infectious diseases. The findings were:

POC-testing is likely to result in health service savings when managing paediatric febrile illness in the ED.

The estimated cost of managing ED admissions citing paediatric febrile illness at the patient level, was £351.52 per patient (95% CI £224.06, £788.22) under the current SOC (existing care), falling to £343.88 per patient (95% CI £142.97, £717.76) in the POC-testing arm. Using frequentist methods, it can be argued that given the overlapping confidence intervals, this is not a significant difference, however, when utilising probabilistic sensitivity analysis, which took account of the expected distribution of costs under each management scenario, there was an 68% likelihood of cost savings from POC testing. At the population-level, considering all estimated annual ED presentations for paediatric febrile illness in the UK, the estimated health-service savings from switching to POC-testing equalled £6.35m. Under base-case assumptions, the cost of POC testing could increase to £17.50 per test and still remain cost-neutral compared to the existing standard of care. As reported in previous chapters, the likely efficiency savings associated with POC-testing differed by age-group, reaching a peak among those aged <6 months. For this group, the savings per

patient of POC-testing equalled £67.82, after taking account of the cost of purchasing any test, falling to £4.25 in those aged >6 months. As such, a great deal of the value which POC-testing is expected to deliver at the population level, can be attributed to the ability to modify care pathways for those aged <6 months, where the actual and perceived risks of serious bacterial infections are greatest.

The impact of POC-testing on antimicrobial prescribing rates.

The findings of chapter 6 suggest that POC-testing among febrile children presenting to the ED would be both more effective and less expensive than the current standard of care in minimising clinically unnecessary antimicrobial prescribing. Antibiotic prescribing decreased by 9% (38% to 29%) as a result of implementing a POC strategy among the entire cohort, suggesting significant opportunities for improvement.

Which factors impacted the cost-effectiveness of POC-testing most? Where could future research add the greatest value?

Numerous sensitivity analysis demonstrated that the factors most influential in shaping the cost-effectiveness of POC testing were, in descending order, the cost of the test, ability to rule in/ rule out bacterial infections, the underlying level of non-bacterial antimicrobial prescribing, and adherence to POC test results. Using probabilistic Monte Carlo simulation, POC testing had a 68% probability of being a dominant strategy compared to usual care (lower costs and reduced antimicrobial prescribing).

Sub-group analysis highlighted that the value of POC testing varied significantly with patient age, with those aged <6 months receiving the greatest benefit, and a 97.9% probability of both cost savings and reductions in antimicrobial prescribing.

How has this thesis contributed to the literature?

This section describes the substantive methodological and evidentiary advances, and other key findings from the studies in this thesis, made in three areas: the economic impact of paediatric febrile illness; preferences for care, and the potential role of POC-testing. The findings are contextualised in relation to the current knowledge base and methodological advances.

Contribution to the knowledge base concerning the economic impact of paediatric febrile illness

Chapter 2 demonstrated a clear evidence gap regarding the economic implications of managing paediatric febrile illness in the ED. While a handful of previous studies had conducted small-scale evaluations of economic impact (C. Byington, C. Reynolds and K. Korgenski, et al. 2012) (Hoberman, et al. 1999) (Iyer, et al. 2006) (D. Schriger, L. Baraff, et al. 2000), these were predominantly focused on US-care settings in limited populations, with no prior studies conducted within the UK. These populations included those at varying ends of the febrile spectrum, from confirmed UTI and meningitis, to laboratory confirmed, community-acquired pneumonia. Two studies did provide an assessment of the cost of managing paediatric febrile illness in children with fever more broadly (C. Byington, C. Reynolds and K. Korgenski, et al. 2012)

(Iyer, et al. 2006), however these analyses were limited to children aged <90 days and <24 months respectively, limiting their generalisability.

As such, the findings of chapter 3, which are based on a full-year cohort of all presentations with fever, of all ages, and all presenting complaints, whether viral, bacterial or other, presents a novel addition to the literature. This study was the first to analyse patient-level costs and healthcare resource use, in a representative sample of febrile children which can be considered representative of the wide spectrum of presentations experienced in routine clinical practice. The finding that short-stay inpatient admission is a key driver of costs is a novel addition to the literature, as is the economic impact of clinically unnecessary antimicrobial prescribing; with children presenting with viral illnesses who received antibiotics incurring 9-fold higher resource use than those who did not. Additionally, the use of a novel methodology (TDABC) provided a previously unknown level of detail concerning the impact of managing paediatric febrile illness in the ED, which included nursing, healthcare assistant and doctor time costs, radiography and laboratory costs, medicines and inpatient costs, and also those associated with administration and facilities management. No previous study had used time-in-motion design, with a stopwatch, to shadow a sample of patients presenting to the ED with febrile illness, to determine all points of interaction with the health service and therefore no study had assessed all overlapping cost components combined. Additionally, no previous study had provided measures of uncertainty (SD, 95% CI or sensitivity analysis) around any of the costs calculated in their respective studies, another first for chapter 3.

Contribution to the knowledge base around preferences for care

Numerous previous studies have examined preferences for emergency care among parents. A systematic review of emergency medicine highlighted that interpersonal skills/staff attitudes; the provision of information, and perceived waiting times are most closely associated with parental satisfaction with care (Taylor and Benger 2004).

Similarly, studies have shown a strong preference for antibiotics in cases of URTIs (Mustafa, Wood, et al. 2014) (Rousounidis, Papaevangelou, et al. 2011), while others have demonstrated a preference for more experienced clinicians managing their children (Chen, Zou and Shuster 2017) (Taylor and Benger 2004). Prior to the work contained within this thesis however, only two studies had assessed preferences for healthcare delivery among parents of febrile children presenting to the ED. These studies focused on preferences for communication among parents of children aged <60 days (Aronson, et al. 2020), and preferences for management of bacteraemia among parents of children aged <3 years respectively (Bennett, et al. 2000). As a result, generalisability to routine cohorts of febrile children of varying ages and presenting complaints was limited. The study presented in chapter 4, therefore represents a novel addition to the existing knowledge base, by focusing on what matters to parents of febrile children and comparing these beliefs with what matters to treating HCPs. While previous studies have demonstrated the disutility associated with prolonged waiting times (Thompson, Yarnold and Williams, et al. 1996) (Thompson, Yarnold and Adams, et al. 1996), a theme also observed within chapter 4, the findings also demonstrated a willingness to extend waiting times by up to 45.6 minutes to avoid pain from investigations, and by 24.1 minutes if this meant being cared for by a

consultant. These trade-offs were previously unknown, the former, perhaps being considered as a proxy for WTW for results of any novel diagnostic.

Furthermore, not only were the findings of this exercise, in this population, a new addition to existing knowledge, but so too was the approach taken. No study to date, in any therapeutic area, had utilised an iterative approach of focus-group, coin-ranking exercise and then DCE, a slight deviation from recommendations by ISPOR (Hauber, et al. 2016), the novel component being the coin-ranking exercise to determine relative preferences, before selecting DCE attributes.

Contribution to the knowledge base regarding the cost-effectiveness of diagnostic advances for the management of febrile illness

While most POC tests undergo clinical performance assessment, very few to date, have evaluated their broader impact on operational, economic, and preference-based outcomes (Verbakel, Turner, et al. 2017). Some studies have evaluated the impact of POC-testing in primary care (Hunter 2015) (Hughes, et al. 2016), however evidence in emergency settings is limited. As such, the real-world value of POC testing in generalisable ED settings is currently unknown. The aim of this economic evaluation was therefore to build upon the findings of the preceding chapters, and determine the cost-effectiveness and perceived value of ED-based POC testing for infectious diseases under a range of care pathway scenarios, including the inclusion of GP-led management as introduced in the previous chapter. The findings presented in this thesis suggest that, under a conservative set of assumptions informed by previously published evidence, POC-testing would be both more effective and less expensive than

the current standard of care in minimising clinically unnecessary antimicrobial prescribing. The addition of GP-led management for non-urgent cases (i.e. GP-management + POC-testing), as recommended in previous studies (Smith, Narang and Ibarz Pavon 2018) (Leigh, Mehta, et al. 2020), can also be expected to reduce both health service costs and antimicrobial prescribing further.

While the study provides an indication that POC-testing is likely to be cost-effective, the study identified several key parameters which affect this conclusion. The factors most influential in shaping the cost-effectiveness of POC-testing were, in descending order, the cost of the test, ability to rule in/ rule out bacterial infections, the underlying level of non-bacterial antimicrobial prescribing, and adherence to POC test results. Despite sensitivity to these parameters, Monte Carlo simulation highlighted that POC-testing had a 68% probability of being a dominant strategy compared to usual care (lower costs and reduced antimicrobial prescribing), increasing to 97.9% among those aged <6 months.

Critique of the overall study design

The strengths and limitations of each study were discussed briefly in chapters 2-6. Below, the strengths and limitations of the overall approach and study design are explored further, focussing on the data sources and methodology.

Key strengths of the datasets

A key strength of the two cross-sectional datasets analysed in chapters 3 and 5 are the level of granularity and variability inherent to each. Additionally, as each dataset was electronically captured and transferred, with no data transformation required, the accuracy and validity of the data was likely maintained, and equivalent to the day and time it was recorded. As we obtained data for all presentations citing febrile illness (chapter 3), and all presentations triaged MTS green or less (non-urgent) in chapter 5, the datasets were not limited or restricted by any means therefore benefitting from considerable variability. Furthermore, the size of each dataset (~6,500 observations in chapter 3) and ~13,000 observations in chapter 5, from year-round observations, including all four-seasons; provided the power to precisely estimate parameters and effect sizes among not just the entire cohorts, but also sizeable sub-populations, stratified by age, gender, MTS status, treating clinician, working diagnosis and clinical parameters such as heart and respiratory rate among others. Furthermore, the preference dataset utilised within chapter 4 could also be considered highly generalisable. We sought opinions from parents across the North West of England, including Huddersfield, Lancashire, and Merseyside, and were able to engage highly variable populations to take part in the study, including a men's darts team, parent

teacher associations, parents within soft play centres and community groups. The diversity of respondents was also a strength. Our sites for inclusion in the focus-groups, coin-ranking exercises and DCEs were stratified to include locations of varying socio-economic status and demographics. As a result, our DCE surveys were designed using pictorial representations to minimise cognitive burden and maximise understanding, which was particularly beneficial among those in whom English was not a first language.

Key limitations of the datasets

Limitations of the datasets used concern generalizability to other settings, with every dataset utilised within the collective works of this thesis collected in Northern England. Furthermore, the prospective clinical data interrogated in chapters 3 and 5 was collected from a single site, with analysis and outcomes based on local prescribing protocols. As such, the conclusions reached may not be generalisable to other settings, where care processes differ from those experienced in our hospital. Another limitation concerns the completeness of our prospectively collected datasets. In chapter 3, approximately 24% of the observations were removed due to missing or incomplete data. While it was assumed that these data were missing at random and likely the result of busy ED staff not finding the time to complete extensive notes for each patient while in the department, this nonetheless could have impacted the findings, leaving questions as to how the results may have differed, if data for these children were available. Additionally, from a parent preference perspective, due to ethical concerns it was decided to seek opinions from members of the general population (who may

have experienced their child having a fever), rather than including parents of children who were currently febrile and recruited in the ED. Although this may be considered a strength in the context of government funded healthcare systems, this could have affected the accuracy of our results due to recall bias, particularly among those whose children were much older (such as the Euxton PTA group). Moreover, sample sizes in the parental and HCP DCEs were limited, which made robust, precise conclusions, particularly among sub-groups, difficult.

Key strengths of the doctorate

The analyses in this thesis have used varying scientific approaches and methodologies, from GLM, to focus-groups, mixed logit regression, economic modelling, and case-control models. This has enabled a multi-perspective analysis of the patient, parent and economic impact of managing paediatric febrile illness in the ED, and the value inherent to improved diagnostic modalities which can reduce diagnostic uncertainty. All methodologies employed were carefully selected, based on their use in other therapeutic indications, and have been performed with reference to existing best practice standards, where possible, endeavouring to add a novel addition to each methodology; whether the use of TDABC in the patient-level costing in chapters 3, 5 and 6, or the use of coin-ranking exercises in chapter 4. Using highly time-consuming but detailed processes such as TDABC, and the multi-phase iterative approach employed during chapter 3 when estimating parental and HCP preferences, provided the opportunity to explore previously un-examined subthemes, at both the patient and HCP level. This enabled targeted and precise conclusions regarding the value, and

recommendations regarding the potential future implementation of novel infectious disease diagnostics.

Key limitations of the doctorate

The novel approaches taken to the collection and synthesis of datasets, while thorough, often led to the combination of several datasets, thereby introducing the opportunity for multiplicative errors. In the case of chapter 3, the combination of a TDABC, which was based on a sample of 71 patients in the ED timed with a stopwatch, was then applied to patient-level data for a further 6,518 patients. Once this was complete, an algorithm adapted by Herberg et al. (Herberg, et al. 2016) was then applied to determine the appropriateness of antibiotic use, and following this, sensitivity analysis applied throughout. The use of multiple, albeit complementary techniques could have introduced small biases, which when combined, may have resulted in imprecision. Additionally, given that most of the findings included in this thesis are based on observational data, there is therefore the potential for confounding due to omission of unobserved variables. The studies included, adjusted for this where possible, by including a broad range of potential confounders, based on observations previously reported in the literature. The use of a natural experiment in chapter 5 for example, although providing balance in terms of baseline characteristics, the findings cannot be considered causative. The gold standard for unbiased evaluation in the ED, is an RCT of any POC diagnostic versus standard care in the ED as demonstrated previously (Hubert, et al. 2020) and the current PRONTO trial in adults (PRONTO 2019). Therefore, due to the observational nature of these analyses, further research,

incorporating causative study designs would be required before definitive conclusions could be made. These studies nonetheless provide the basis for such studies. Finally, while every effort was made to be as inclusive as possible, it is entirely likely that important data were omitted from our analyses. In the case of chapter 4, the iterative deletion of attributes in order to meet the methodological requirements of a DCE, following the coin-ranking exercise, means that attributes deemed important in the literature (and among the focus-group), were not included. Because the ranking may have been different in other populations, it is therefore possible that factors which are influential in determining satisfaction with care were omitted, an issue which future research should aim to address.

Conclusions

Paediatric fever is one of the most common causes of ED attendance, but despite its frequency, it remains a diagnostic conundrum. Though most children will suffer from self-limiting viral illnesses, both viral and severe bacterial infections will often result in similar clinical presentations. Coupled with an absence of timely and sufficiently sensitive diagnostics to aid real-time clinical decision making, a cautious approach to the management of the febrile child is common. This entails both parental and HCP dis-satisfaction, while also driving potentially avoidable resource use and antimicrobial prescribing.

Both parents and healthcare providers have expressed strong desires for what they believe is important when caring for a child with febrile illness in the ED. This

includes a strong proclivity for reducing waiting times, providing clinical results and reassurance faster, minimising unnecessary pain from investigations, and reducing use. However, based on the suboptimal existing diagnostics employed during the management of paediatric febrile illness; where possible at all, these outcomes are often traded-off against one another, leaving a significant opportunity for improvement. Supplementing existing care processes with promising approaches to managing febrile illness and other non-urgent conditions, including anticipated POC tests, and GP-led care, may therefore be able to unlock significant patient, parent, and health-service benefits. The findings presented here suggest that the combination of both GP-led care, and POC-testing to identify febrile aetiology, would not only be cost-effective, but also enable proportionate, and evidence-based management from admission to discharge. Given the recent move towards integrated care systems (ICSs) within the NHS, this collaborative approach to care can be expected to improve satisfaction with care significantly. The value of such interventions, while considerable for all, reaches a peak in those aged <3months, supporting the need for targeted (or early-stage use) in this group.

Policy recommendations

The findings of this thesis highlight several key areas of discussion, which if explored further at the health policy level, may increase the likelihood of success when both evaluating and implementing novel POC technologies in the future. The first policy consideration concerns the topic of willingness-to-pay for reductions in antimicrobial prescribing. AMR has developed as one of the major and most urgent threats to public

health (WHO, 2016). But while researching novel antimicrobial agents can often dominate discussions around AMR, presently there are few incentives for pharmaceutical manufacturers to dedicate their efforts to the development of modern antimicrobial therapies (Simpkin, Renwick, & Kelly, 2017) (Dutescu & Hillier, 2021). This emphasizes the importance of paying more attention to diagnostics, including POC-testing and PCR tests, which have gained a lot of attention with respect to Covid-19 in the past year.

However, as demonstrated in this thesis, when focused predominantly on short-term financial considerations, novel diagnostics may not initially be cost saving, or even cost neutral, instead potentially imposing additional pressures on already limited healthcare budgets. Similarly, health policy makers may not consider AMR as significant a problem as shortfalls in healthcare funding, instead preferring improvements in health service efficiency today, at the expense of increases in antimicrobial prescribing and AMR tomorrow. Willingness-to-pay for reductions in antimicrobial prescribing is therefore an important consideration, as with the exception of infants where economic savings were significant, it is likely that additional funding may be required in the short term to tackle this problem.

These costs may not only be limited to those associated with the procurement of POC tests, but also ensuring sufficient opportunity for rigorous evaluation, including randomized controlled trials. As an example, the NIHR Health Technology Assessment-funded PRONTO randomized controlled trial, is evaluating whether the addition of POC Procalcitonin measurement to National Early Warning (NEWS2) scoring can lead to a safe reduction in intravenous antibiotic initiation in adult ED

patients managed as suspected sepsis, compared to NEWS2 scoring alone (PRONTO 2019). If such RCTs are not possible, particularly given the financial toll of the COVID-19 pandemic, questions regarding how much the NHS is willing to pay to combat AMR would be of considerable value.

In England, for example, the National Institute for Health and Care Excellence (NICE) has made the decision to allow a higher cost-effectiveness threshold for treatments that provide short life extensions to terminally ill patients (NICE, 2009), with similar agreements in place for orphan disease treatments. Reductions in antimicrobial prescribing may therefore need to be valued greater than the sum of their immediate tangible health improvements, in order to prioritise and guarantee their implementation. However, decisions concerning the societal valuation of health outcomes are ultimately the decision of the public, as it is society that bears the costs of any decision. If the prioritization of technologies to reduce antimicrobial prescribing are to be considered, including POC testing, public consultation on the societal value of combatting antimicrobial resistance should first be sought.

If novel technologies are to be funded, our second policy recommendation is that all healthcare facilities have access to these technologies (primary, secondary and tertiary care), and are provided support and guidance to eventually incorporate them to the degree that they are considered common practice. This includes ensuring that access to multiplex molecular panels are not dependent upon a facility's location, size or patient demographics, thereby restricting access and reducing equity.

Our third recommendation is that regulatory bodies place greater importance on the evaluation of such tests, even considering accelerated review and adoption processes,

as previously observed with NHS England's Cancer Drugs Fund (Leigh & Granby, 2016), and the European Medicines Agency's adaptive pathways model (EMA, 2014), when possible. With any novel technology, whether pharmaceutical or medical device, assessment by health regulators to explore cost-effectiveness is a critical step prior to implementation. Economic models can take significant time to research, develop and quality assess, which in the event of antimicrobial prescribing may result in an opportunity cost in terms of extended exposure to the risks of AMR while such evaluations are undertaken. It is therefore our final recommendation that health regulators, particularly within the United Kingdom, including NICE, the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) consider utilizing the model presented in this thesis to inform or streamline assessment of such technologies.

Further research

In addition to several policy recommendations the chapters in this thesis have also highlighted several areas requiring further research, with the sections above outlining these opportunities in greater detail. It is clear throughout the works of this thesis that much could be learned through additional study of the themes covered, in alternative settings, where healthcare provision and care pathways differ to those experienced in the UK. Additionally, while the results presented here suggest that novel diagnostics will provide the opportunity to incur considerable operational, clinical, patient-centric, and economic benefits, these findings should be confirmed using causative study designs. Well designed, adequately powered multi-centre RCTs which include

economic evaluation and qualitative assessment, which compare POC diagnostic supported assessment with standard care in febrile children presenting to the ED will be essential. A similar trial is currently being conducted in adults with suspected sepsis in the UK, details of which can be found at https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/pronto (PRONTO trial 2020). Furthermore, any such analyses should consider the multitude of factors shown to impact care provision and outcomes as demonstrated here, including patient age, clinical experience and MTS classifications.

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