The adoption of rapid diagnostic tests for the clinical management of acute childhood infections in European settings.

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Declaration of own work

I, Juan Emmanuel Dewez, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: Juan Emmanuel Dewez Date: 21/04/23

Abstract

Introduction

Rapid point-of-care diagnostic tests (POCTs) have been widely advocated to improve the use of antibiotics and medical resources. The extent of the adoption of POCTs for the clinical management of acute childhood infections in European countries and the determinants of adoption are unclear.

Aim and Objectives

The aim of this thesis is to address evidence gaps about the factors which contribute to the adoption of POCTs for the clinical management of acute childhood infections in European settings.

Objectives:

- *Objective 1*: To estimate the variability in the availability and use of POCTs for the clinical management of acute childhood infections across European countries.

- *Objective 2:* To explore the determinants of this variability across European countries.

- *Objective 3:* To generate an in-depth understanding of the factors that contribute to high- versus low-level availability of C-reactive protein (CRP) POCTs in primary care settings in two countries with similar primary healthcare systems, and to explore whether the tests are used in children.

- *Objective 4*: To generate an in-depth understanding of the factors that contribute to the different levels of availability and use of CRP POCTs in hospitals in these two countries.

Methods

A mixed methods approach was used to meet these objectives:

- *Objective 1*: Quantitative cross-sectional survey of European primary care and hospital paediatricians.
- *Objective 2*: Multilevel logistic regression analyses to assess the contribution of explanatory factors to the adoption of POCTs at two levels: 1) workplace and clinician level, and 2) country of work level.

- *Objective 3:* Comparative qualitative case studies at primary care level, based on documents analysis and in-depth interviews of stakeholders in the Netherlands and England. The study was informed by the non-adoption, abandonment, scale-up, spread and sustainability (NASSS) framework.

- *Objective 4:* Comparative qualitative case studies at hospital level, based on documents analysis and in-depth interviews of stakeholders in the same countries. The study was also informed by the NASSS framework.

Results

- *Objective 1:* 2342 paediatricians from 29 European countries took part in the cross-sectional survey. The availability and use of the nine POCTs included in the survey vary substantially across Europe.

- *Objective 2:* The country of work better predicts the availability and use of POCTs than workplace or healthcare workers characteristics.

- *Objective 3:* 65 documents were identified, and 21 interviews were conducted. CRP POCTs are more widely available in primary care in the Netherlands than in England mainly because of the interplay between early adopters and factors at the macro level of health systems. These factors include the existence of a fee-for-service reimbursement scheme, the better integration of health services, and the lower funding constraints in the Netherlands. In both countries CRP POCTs are used less frequently in children than in adults because of the perceived uncertainty regarding the accuracy and effectiveness of using these tests in children, the lack of guidelines, and the perceived invasiveness of finger pricking.

- *Objective 4:* 41 documents were identified, and 46 interviews were conducted. The main contributors to the higher adoption of CRP POCTs in hospitals in the Netherlands lie at the micro and macro levels. Most hospital healthcare workers in the Netherlands are familiar with CRP POCTs and trust the tests because they are widely used in primary care. Moreover, hospital funding is more limited in England. Most hospitals in the Netherlands and England have not adopted CRP POCTs because the hospital laboratory is able to provide laboratory-based CRP results in a few hours at a lower cost.

Conclusion

The adoption of POCTs is a complex phenomenon even though the technology itself appears to be relatively simple and easy to use. The adoption of POCTs for the management of acute childhood infections varies substantially across Europe. Factors at the macro level of health systems are more influential overall in determining the adoption of POCTs. Differences in reimbursement mechanisms, the integration of health services, overall expenditure on healthcare, and healthcare workers' trust are the main contributors towards the greater adoption of CRP POCTs in the Netherlands compared to England. The specific factors that contribute to the adoption of CRP POCTs and other POCTs in other countries with different health systems structures and processes may be different. Should these POCTs and future POCTs be implemented, understanding these factors would be essential for informing their implementation.

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Preface

I grew up in Bolivia, Belgium, and Haiti. I have always been touched by the healthcare needs in some of these countries. Thus, I decided to become a medical doctor. I specialized in paediatrics and then in tropical medicine and international health.

I have worked as a clinician, as a manager of healthcare programmes, and as a researcher in several countries of Africa, the Caribbean, and Asia. During my professional experience I often wondered whether medical innovations would improve healthcare and whether their implementation would be possible in low- and middle-income settings.

In 2017, I joined the PERFORM-DIAMONDS consortium, a European research consortium aiming to improve the management of children with acute fever by developing novel diagnostic tests. Although the consortium focused on European countries, I felt that the diagnostic tests the consortium was developing could also be useful for low- and middle-income countries in the medium to long term.

Within PERFORM, I was part of a work package which aimed to study the potential costs, risks, and benefits of introducing the novel diagnostics in different European healthcare settings. More specifically, I worked on a comparative health systems analysis of European countries to inform the most appropriate approach to introduce the new diagnostic tests. This thesis is based on most of this work.

Structure of the Thesis

This thesis is structured in the style of a research paper. It is comprised of three papers, as well as an introduction, a methods section, an overall discussion, and linking material.

The first chapter is an introduction which provides an overview of the importance of acute infections in the daily routines of healthcare workers who provide care to children. This chapter also introduces the role of diagnostics, including POCTs, in helping healthcare workers to treat children with acute infections. This chapter includes a systematic review of the current literature on the adoption (including the availability and use) of POCTs for the management of acute childhood infection in European countries.

Chapter 2 presents the aim and objectives of the thesis.

Chapter 3 presents the theoretical frameworks which have informed the design of the three studies which form the basis of this thesis, as well as providing a summary of the methods used in each study.

Chapter 4 (Research Paper 1) aims to address the paucity of data about the availability and use, and their determinants, of POCTs for the management of acute childhood infections in European countries. It examines a cross-sectional survey of paediatricians and includes multilevel regression analyses to identify these determinants.

Chapter 5 (Research Paper 2) aims to provide an in-depth understanding of the factors that contribute to the difference in the level of adoption of a specific POCT (C-Reactive Protein) in primary care in two countries that share health systems characteristics but have different levels of POCT implementation. It consists of qualitative comparative case-studies.

Chapter 6 (Research Paper 3) aims to provide an in-depth understanding of why the adoption of C-reactive protein POCTs is also different in these two countries but with the focus this time on hospitals, given that the organisation of hospital care is different from that of primary care. It also consists of qualitative comparative case-studies.

Chapter 7 provides a summary and synthesis of the key findings of the thesis. It includes a discussion about the contribution of this work to the goal of obtaining a greater understanding of the factors that contribute to higher and lower rates of POCTs adoption. This chapter also suggests recommendations about what is needed to implement POCTs in European countries, and highlights areas that warrant further research.

Chapter 8 is a summary of my personal reflections.

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List of Acronyms and Abbreviations

AHSN	Academic Health Sciences Network
AMR	Antimicrobial Resistance
AUC	Area under the receiver operating characteristic curve
AXIS	Appraisal tool for Cross-sectional Studies
CCG	Clinical Commissioning Group

CE	Conformité Européenne
Covid-19	Coronavirus disease 2019
CRP	C-reactive protein
DAG	Direct acyclic graphs
DIC	Deviance information criterion
DIAMONDS	Diagnosis of Febrile Illness using RNA Personalised Molecular Signature Diagnosis
DOT-DBC	Diagnosebehandelcombinatie (Dutch Diagnosis Related Group)
DRG	Diagnosis Related Group
EAPRASnet	European Academy of Paediatrics Research in Ambulatory Settings network
ECDC	European Centre for Disease Control
ED	Emergency Department
ESPID	European Society of Infectious Diseases
EU	European Union
EFTA	European Free Trade Agreement
FBC	Full blood count
GAS	Group A streptococcus
GDP	Gross Development Product
GP	General Practitioner
HEC	Health expenditure per capita
HTA	health technology assessment
IQR	Inter quartile range
IOR80	80% interval odds ratio
LSHTM	London School of Hygiene and Tropical Medicine
MCMC	Markov chain Monte Carlo methods
MeSh	Medical subheadings
NASSS	Non-adoption, abandonment, scale-up, spread and sustainability framework
NHG	Dutch Royal College of General Practitioners
NHS	National Health Service
NICE	National Institute for health and Care excellence
NVK	Dutch Royal College of Paediatricians
NZA	Dutch Healthcare Authority

OECD	Organisation for Economic Co-operation and Development
OR	Odd ratio
POCTs	Point of care tests
PERFORM	Personalised Risk assessment to optimise Real-life Management across the Europe
POCTs	Point of care tests
PCT	Procalcitonin
RCPCH	Royal College for Paediatric and Child Health
REPEM	Research in European Paediatric Emergency Medicine network
RSV	Respiratory syncytial virus
UD	Urine dipstick
UK	United Kingdom
WHO	World health Organization

Glossary

Adoption: In this thesis, adoption is defined as the decision of a healthcare organisation or healthcare workers to make an innovation available and to use it.

Point-of-care tests (POCTs): In this thesis, POCTs are defined as in vitro rapid diagnostic tests that can help frontline clinicians to make clinical decisions during the consultation timeframe. Thus, the focus is on POCTs which analyse body fluids, can be operated by frontline clinicians, do not require laboratory expertise, and can provide results in ~15 minutes.

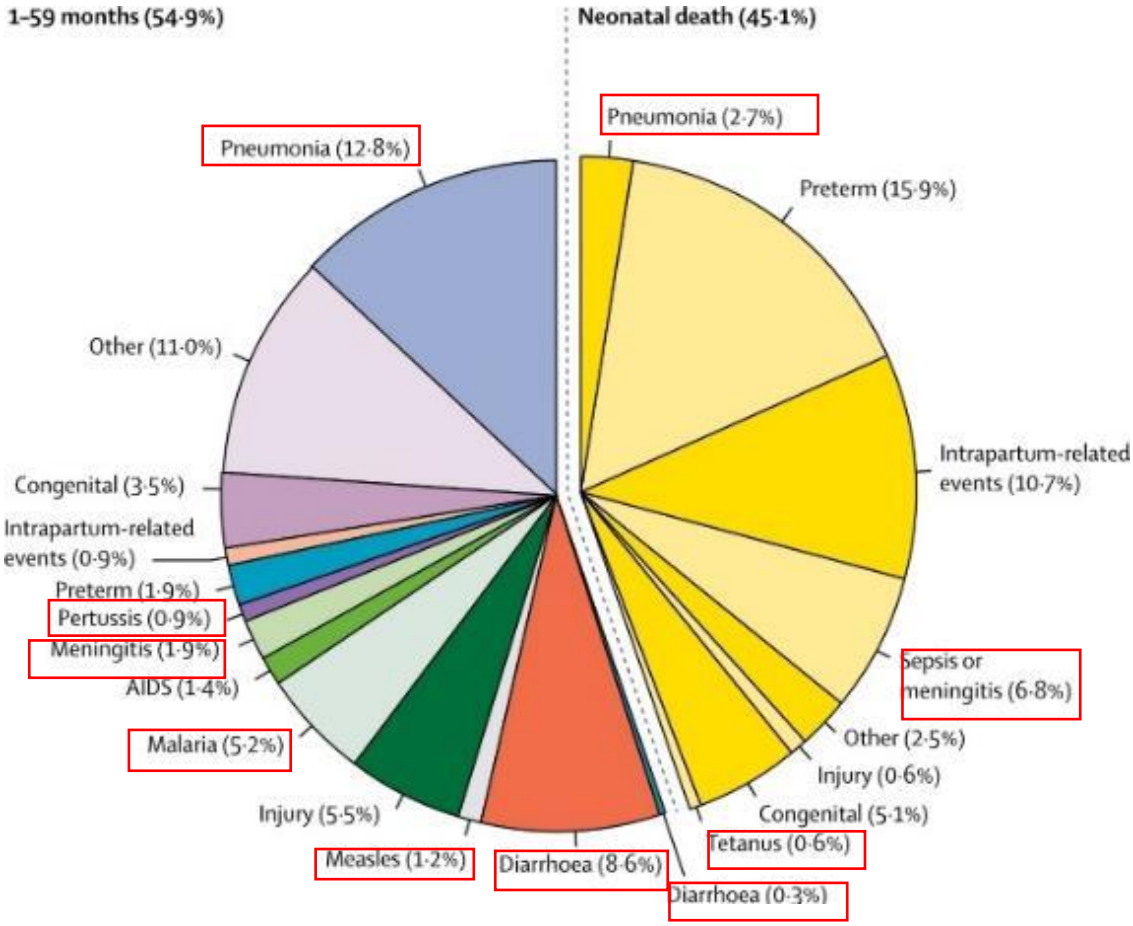
Chapter 1. Introduction

1.1. The burden of acute childhood infections

Acute childhood infections are a frequent reason for seeking healthcare. Fever is a common manifestation of acute infections. In European settings, it is estimated that under-five children present on average two episodes of fever per year.[1,2] Most parents consult at primary care level for at least one episode of infection per year.[3] Some febrile children are brought to hospitals: up to 25% of the attendance in emergency departments and 20% of paediatric hospital admissions are for the management of children with fever.[1,4]

Acute childhood infections are a major cause of mortality. Recent estimates suggest that acute infections cause 41% of under-five deaths globally (Figure 1) and 10% of deaths in high-income countries (Figure 2).[5]

Figure 1. Global under-five cause-specific mortality estimates

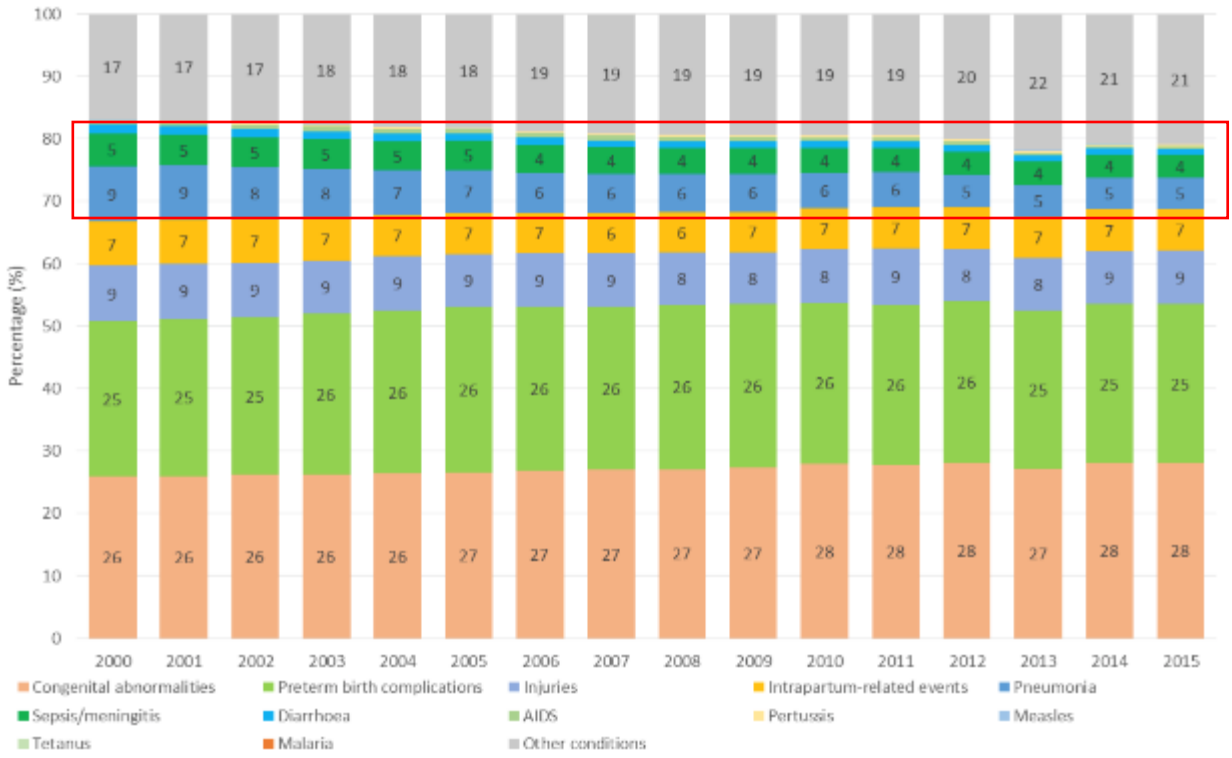


Adapted from Liu et al.[5]
The red outlines highlight the mortality caused by acute infections

However, most febrile children have self-limiting infections. In European settings, severe bacterial infections represent less than 1% of febrile children attended to in primary care,[6] and 7-15% of those presenting to hospitals.[7,8]

Distinguishing severe bacterial infections from common self-limiting infections in children is difficult, particularly in young infants. This is because the clinical features of infections in children are often non-specific,[6] which generates substantial diagnostic uncertainty amongst healthcare workers who provide healthcare to children.

Figure 2. Under-five cause-specific mortality estimates in high income countries



Adapted from Liu et al.[5]
The red rectangle highlights the proportion of mortality caused by acute infections.

1.2. The role of in vitro diagnostics in the clinical management of acute childhood infections

Diagnostic tests are medical tests that are carried out to help diagnose a condition, disease, or illness. The main types of diagnostic tests are:

- Check lists or questionnaires to identify symptoms

- Diagnostic tests or manoeuvres during physical examinations to identify signs of disease
- Image-based diagnostic such as X-Rays to identify anomalies in specific parts of the body
- In vivo diagnostics for imaging or monitoring different parts of the body
- In vitro diagnostics to study a sample of tissue or body fluids (such a blood or urine)

Diagnostic tests can help to reduce diagnostic uncertainty by identifying the site of infection (e.g., chest x-rays can identify lung infections), the potential causal pathogen (e.g., microbiology tests can identify bacteria in blood or other body fluids), or by measuring the patient's response to infection (e.g., some diagnostics can measure inflammatory markers).

This thesis focuses on in vitro rapid diagnostic tests. In vitro diagnostic tests are usually available in laboratories. Primary care practices are rarely equipped with a laboratory. Thus, primary care healthcare workers wishing to use in vitro diagnostics need to send samples to external laboratories. However, this requires some degree of infrastructure to send samples and obtain results. The results from the tests may also not be available on the day of the consultation. Because of this, primary care healthcare workers often manage their patients without this type of diagnostics. In febrile children, the combined diagnostic uncertainty and the fear of missing severe bacterial infections can result in the empiric use of antibiotics.[9]

In hospitals, in vitro diagnostic tests are usually available at the hospital's laboratory. The turnaround time for diagnostic results varies from a few hours to up to several days for tests which require cultures to grow to identify pathogens. Healthcare workers often use several diagnostic tests (some of them being invasive, such as lumbar punctures), admit children (particularly young infants) while waiting for test results, and prescribe broad-spectrum antibiotics which are not always justified. This approach results in anxiety and discomfort for the children and their parents and also makes unnecessary use of health services' resources.[10] Moreover, the overuse of antibiotics may contribute to the development of antibiotic resistance, which is a global health concern.[11]

1.3. The role of point-of-care tests in the clinical management of acute childhood infections

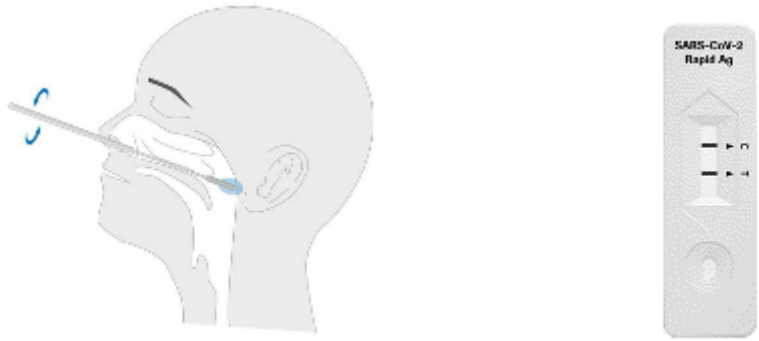
Rapid point-of-care tests (POCTs) are diagnostic tests that can be performed and processed at the point of care and can provide results rapidly.[12] There is no consensus about how rapid a test's turnaround time should be for the test to be qualified as a rapid POCT. The World Health Organisation (WHO) definition of a rapid turnaround time is between 15-60 minutes.[13] However, some more complex POCTs, such as polymerase chain reaction POCTs, can have a turnaround time greater than 30-60 minutes. Some POCTs are easy to operate, and some are even performed by the patients themselves, such as pregnancy tests or tests to detect SARS-Cov2. Other POCTs are more complex and need samples to be prepared, usually by a qualified laboratory technician, before they are analysed. Because of this, these tests are usually used in laboratory settings even though they could in theory be used at the point of care. Moreover, in some hospitals, the use of POCTs is sometimes restricted to laboratory settings because the laboratory department prefers to centralise the use of all diagnostics to ensure its results are reliable and comply with quality standards. In this scenario, POCTs are not used at the point of care.

This thesis focuses on POCTs that can help frontline clinicians to make clinical decisions during the consultation timeframe. Thus, the focus is on POCTs which are easy to operate, do not require laboratory expertise, and are able to provide results in ~15 minutes.

Most POCTs are in vitro diagnostics which analyse body fluids such as blood, urine, or nasal secretions. Among these POCTs, there are three main types of tests that can be used for the management of acute childhood infections. The first are POCTs that detect the presence of a specific pathogen. This includes tests which detect SARS-Cov2 (Figure 3A), Group A Streptococci, or malaria parasites.[14-16] A limitation of these tests is that they can only detect one pathogen even if there are multiple pathogens causing infections, and some pathogens are present in sites that are difficult to access (e.g., central nervous system and lungs). The second type are rapid tests which measure the patient's reaction to infection by measuring inflammatory markers such as the C-reactive protein (CRP) (Figure 3B) or procalcitonin (PCT).[17] These biomarkers are particularly useful in febrile children with no other clinical signs as they may help to rule-in or out severe infections even if the pathogen and/or the location of infection is not identified. However, it can take 8 to 36 hours for these biomarkers to rise after the onset of disease to levels that can alert clinicians about a potentially severe infection.[18] The third type of POCTs are tests that detect the presence of pathogens and the host reaction to infection, such as urine dipsticks (Figure 3C). These tests can indicate the

presence of nitrites produced by gram negative bacteria in the urine of patients with a urinary infection, as well as leucocyte esterase which are enzymes that are produced by the patient's white cells in reaction to infection.[19] Urine dipsticks are useful to diagnose urinary tract infections, but they can neither identify the specific pathogen causing the infection, or its sensitivity to antibiotics.

Figure 3. Types of point-of-care tests which can be used by frontline healthcare workers



A

B

C

A: SARS-Cov2 point-of-care test. Source: Roche diagnostics
B: C-reactive point-of-care test. Source: Abbott diagnostics
C: Urine dipstick point-of-care test. Source: Sykepleien.no

There are other POCTs which are not in vitro diagnostic tests, such as pulse oximeters which measure blood oxygen saturation by measuring the skin colour of fingers exposed to artificial light. The scope of this thesis is limited to POCTs which are in vitro diagnostics, however.

In primary care, POCTs could help to solve the logistical issues of sending sample to an external laboratory. POCTs which can identify patients who should be treated with antibiotics may allow for a more targeted use of these medicines.
In hospitals, the use of POCTs outside of the laboratory, i.e., in clinical wards, may help in expediting patient care. POCTs which can identify patients at risk of severe deterioration may help to better identify the patients who need to be admitted and for whom additional diagnostic tests are needed. This may result in a better use of health services resources.[20]

The WHO, together with several European countries, has recommended the use of rapid POCTs to improve the use of antibiotics in relation to their antimicrobial resistance policies.[21,22]

The impact of POCTs depends on their analytical performance (including the minimum amount of biomarker or pathogen material they can detect, the measurement range, and the measurement accuracy), clinical performance (i.e., the ability to detect patients with a particular clinical condition), and the cost-effectiveness of using the tests in a given care pathway (i.e., whether they are good value for money compared to alternative care).[23] There are several POCTs which can be used in the clinical management of acute infections in children, but their impact varies and they are still being assessed.[24] The impact of POCTs also depends on the adoption of the tests by healthcare workers and health services, which, in turn, depends on factors such as user friendliness and whether the use of the tests changes clinical practices. In this thesis, adoption is defined as the decision of a healthcare organisation or healthcare workers to make an innovation available and use it.[25]

In terms of the availability and use of rapid POCTs for the clinical management of acute infections, recent studies suggest that POCTs are available in Northern European countries, as well as in Germany and Switzerland.[26,27] However, these studies focussed on adult care in primary care settings. Whether POCTs are used in children in those countries and in other European countries is unclear.

1.4. The adoption of point-of-care tests for the clinical management of acute childhood infections in European countries: a systematic review of the literature

1.4.1. Aim

The aim of this systematic review was to assess the extent of the adoption of POCTs which can be used in the clinical management of acute childhood infections in European countries, and to explore the determinants of these adoption levels.

1.4.2. Objectives

1. To estimate the availability and use of POCTs for the clinical management of acute childhood infections in European countries.
2. To identify the determinants in the availability and use of these POCTs.

1.4.3. Methodology

1.4.3.1. Inclusion criteria for considering studies for this review

Types of studies

Studies reporting the availability and/or use of rapid POCTs for the management of acute infections in primary care and hospitals.

Types of participants

Given that some POCTs can be used in both adults and children and that in some countries general practitioners (GPs) and emergency departments (EDs) provide healthcare to both adults and children, studies focusing on adults and/or children were included.

Types of outcome measures

- The availability of POCTs for the clinical management of infections in primary care practices or hospitals.
- The use of POCTs in children presenting with an acute infection.
- The determinants of the availability and use of POCTs in the management of infections.

Types of POCTs

Studies which report on the availability and use of the following POCTs were included:

1. Urine dipstick
2. Group A streptococcus (GAS) POCT
3. Respiratory syncytial virus (RSV) POCT
4. Influenza POCT
5. Full blood count (FBC) POCT
6. Procalcitonin (PCT) POCT
7. C-reactive protein (CRP) POCT
8. Blood gas POCT
9. Lactate POCT

These POCTs were selected based on a scoping review of the existing literature and discussions between colleagues and the PhD candidate working for the same research consortia (PERFORM and DIAMONDS).[28] Discussions were held during regular consortia meetings with paediatricians from 11 countries (Austria, Belgium, France, Germany, Greece, Latvia, the Netherlands, Slovenia, Spain, Switzerland, and the United Kingdom). The focus was on POCTs which can help frontline paediatricians in primary care and in hospitals to make clinical decisions during the consultation timeframe (~15 minutes). We selected POCTs which were used by frontline paediatricians in at least one European country, based on our knowledge of clinical practice in the eleven countries.

Included countries

All countries which are members of the European Union (EU) or European Free Trade Area (EFTA), in addition to the United Kingdom were included.

1.4.3.2. Search methods for identification of studies

The search was based on the combination of the following domains of enquiry:

1. Adoption (i.e., availability and/or use)
2. Point-of-care tests
3. The nine tests outlined above
4. The countries outlined above

Electronic search

A systematic search of the following five databases was carried out in November 2019:

1. Embase
2. Medline
3. Scopus
4. CINAHL Plus
5. Web of Science

The search was based on a combination of medical subheadings (MeSh), key words, and synonyms for each of the four domains of enquiry (see Appendix). There were no language restrictions. The search was restricted to between 2003 (the year of the first regulatory approval for CRP POCTs, one the most studied biomarkers for the management of infections) and 2019.

Searching of reference lists

The reference list of reports which were assessed for eligibility during the electronic search were also searched to identify additional studies.

1.4.3.4. Data collection and analysis

Endnote X9® was used to screen and manage the findings of the search.

Selection of studies

The PhD candidate screened the titles and abstracts of each record identified in the searches. The full text of studies meeting the inclusion criteria were included in the final analysis. The reasons for exclusion were recorded. The process is presented as a PRISMA flow diagram in the results section (Figure 4).

Data extraction and management

Data were extracted by the PhD candidate using a data extraction form purposively developed to extract the main characteristics of the study and the outcomes of interest.

Assessment of the quality of included studies

Each included study was assessed by the PhD candidate using the Appraisal tool for Cross-sectional Studies (AXIS).[29] The AXIS tool was developed through the consensus of experts in epidemiology, evidence-based medicine, and public health to aid the inclusion of cross-sectional studies in systematic reviews, guidelines, and clinical decision-making. The tool appraises the study design and reporting through the assessment of 20 quality domains (Figure 5).

Data analysis and synthesis

Outcome data were analysed per country. The data were analysed descriptively except when there was more than one study per country, in which case a meta-analysis was conducted. Estimates, with 95% confidence intervals (CIs) were computed for pooled estimates. Random-effect models were used when there was substantial heterogeneity, i.e., when I^2>50%,[30] and while fixed-effects were used when there was moderate heterogeneity. Pooled estimates were plotted as forest plots.

The analysis was synthesised to presents the availability and use of POCTs per country, as well as the determinants of availability and use, when available.

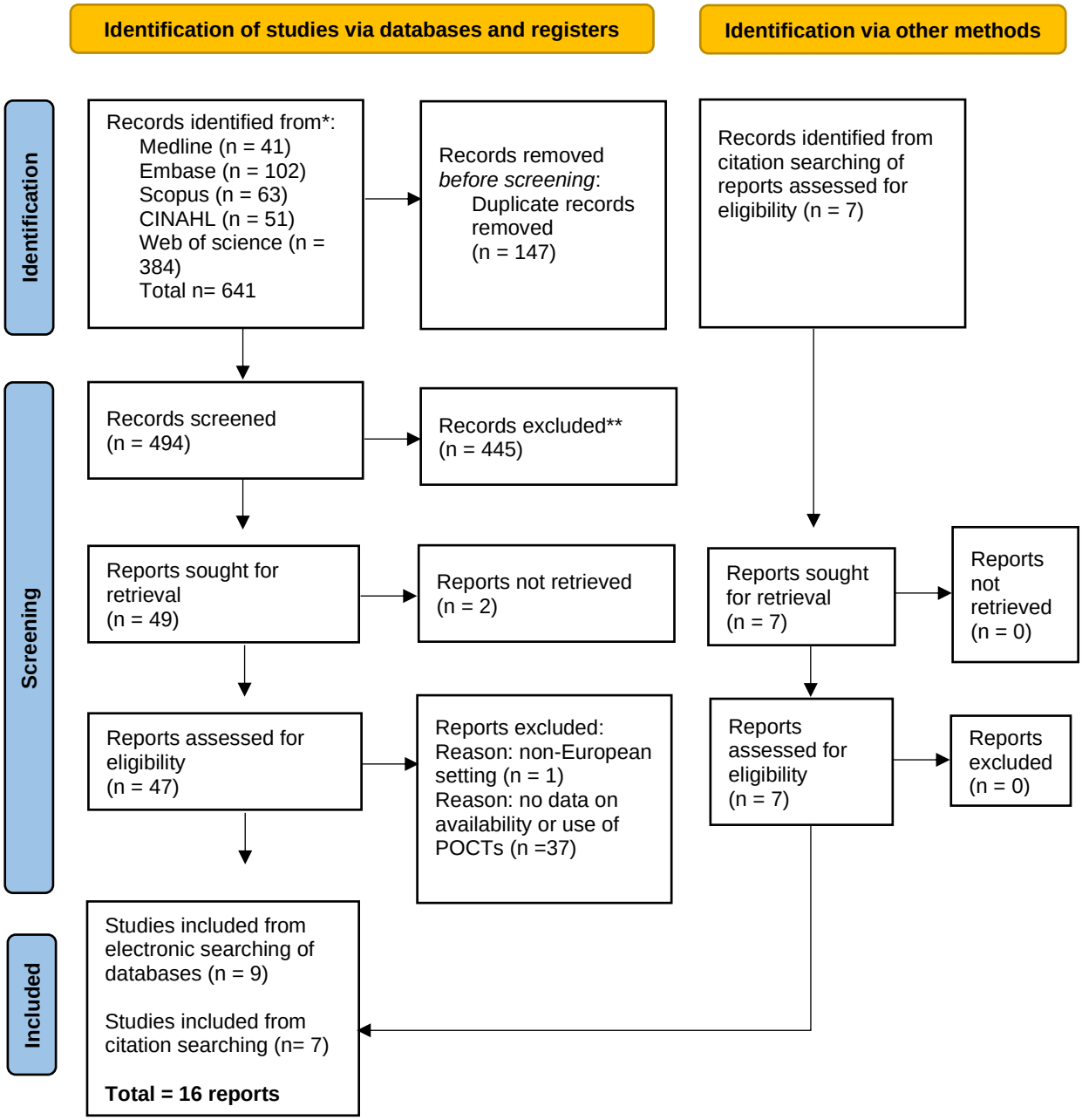
1.4.4. Results

1.4.4.1. Description of studies

Results of the search

The electronic search resulted in 641 records. 147 duplicates were removed. The PhD candidate screened 494 records. 49 records were sought for retrieval. Two records could not be retrieved. The full text of 47 records were assessed. One record was excluded because the data pertained to a non-European country, while 37 other records were excluded because they did not provided data on the availability or use of POCTs. Nine records were included from the electronic search. An additional seven records were identified through the search of references. 16 reports in total were finally included (Figure 4).

Figure 4. PRISMA flow diagram



Characteristics of included studies

The 16 included studies were cross sectional-studies. The studies varied in design, country, and population of interest. Five studies were surveys of GPs. 11 studies were assessments of clinical cases managed in GP practices (Table 1). Of these, six were retrospective and five were prospective studies; four studies used data from national or regional databases which contained data from all GP practices of a given geographic area, and seven studies were based on case records from a sample of GP practices. 13 studies were conducted in a single country, while three studies were conducted across several countries. Studies were conducted in Sweden (6), the Netherlands (3), France (3), Norway (2), Belgium (1), Denmark (1), Germany (1), Latvia (1), Lithuania (1), Poland (1), Switzerland (1), and the UK (1). Of the patient cases reported in the studies, the patients were adults in three of the studies, both adults and children in ten of the studies, and children in three of the studies. The POCTs that were the object of the studies were CRP POCTs, GAS POCTs, and Urine dipsticks.

Table 1. Characteristics of the studies included in the literature review

Study	Study design and period of data collection	Country and setting	Data source and sample size	Scope	Patients	POCTs	Data on availability of POCTs	Data on determinants of availability	Data on use of POCTs	Data on determinants of use
Kip, 2017[31]	Cross-sectional survey of GPs; 2015	Netherlands; GP practices	Responses from GPs; 126 participants	National	Children and adults	CRP, UD	Quantitative estimates	Quantitative estimates	_	_
Haldrup, 2017[32]	Retrospective assessment of GP consultations; 2004-2013	Denmark; GP practices	Healthcare utilisation database: data from 20,162,938 consultations	National	Children and adults with a suspicion of infection	CRP, GAS, UD	Anecdotical evidence	_	Quantitative estimates	Quantitative estimates
Frese, 2016[33]	Cross-sectional survey of GPs; 2009	Germany; GP practices	Responses from GPs; 94 participants	Regional (Saxony)	Adults	CRP	_	_	Quantitative estimates	_
Schols, 2016[34]	Cross-sectional survey of GPs; 2014	Netherlands; out-of-hours GP practices	Responses from GPs; 117 participants	National	Children and adults	CRP, UD	Quantitative estimates	_	_	_

Tyrstrup, 2016[35]	Retrospective assessment of GP consultations; 2013	Sweden; GP practices	Healthcare utilisation database; data from 318, 976 consultations	National	Children and adults with respiratory infections	CRP	Anecdotical evidence	_	Quantitative estimates	_
Howick, 2014[26]	Cross-sectional survey of GPs; 2012-2014	Belgium, Netherlands, and UK; GP practices	Responses from GPs; 2,770 participants	International (Northern Europe)	Children and adults	CRP, GAS, UD	_	_	Quantitative estimates	_
Rebnord, 2015[36]	Retrospective assessment of GP consultations; 2009-2011	Norway; GP practices	Healthcare utilisation database: data from 2,552,600 consultations of children 0–5 years	National	Children	CRP	Anecdotical evidence	_	Quantitative estimates	Quantitative estimates
Streit, 2015[37]	Prospective cross-sectional assessment of GP consultations; 2013	Switzerland; GP practices	Case records; 315 consultations with 39 different GPs	Local (Bern)	Adults with cough	CRP	Anecdotical evidence	_	Quantitative estimates	_

Strumilo, 2014[38]	Prospective cross-sectional assessment of GP consultations; 2012	Latvia, Lithuania, Poland, and Sweden; GP practices	Case records; 13,106 consultations	International (Baltic countries)	Children and adults with respiratory infections	CRP, GAS, UD	_	_	Quantitative estimates	_
Michel-Lepage, 2014[39]	Retrospective cross-sectional assessment of GP consultations; 2012	France; GP practices	Case reports; 1,126 consultations	National	Children with sore throat	GAS	Anecdotical evidence	_	Quantitative estimates	Quantitative estimates
Oppong, 2013[40]	Prospective cross-sectional assessment of GP consultations; unclear period	Sweden and Norway; GP practices	Case records; 370 cases	International (Northern European countries)	Adults with cough	CRP	Anecdotical evidence	_	Quantitative estimates	_
Pulcini, 2012[41]	Cross-sectional survey of GPs; 2011	France; GP practices	Responses from GPs; 369 participants	Regional (PACA region)	Children with sore throat	GAS	Quantitative estimates	_	Quantitative estimates	Quantitative estimates
Neumark, 2010[42]	Retrospective assessment of GP	Sweden; GP practices	Healthcare utilisation database;	Regional (Kalmar county)	Children and adults with	CRP, GAS	Anecdotical evidence	_	Quantitative estimates	_

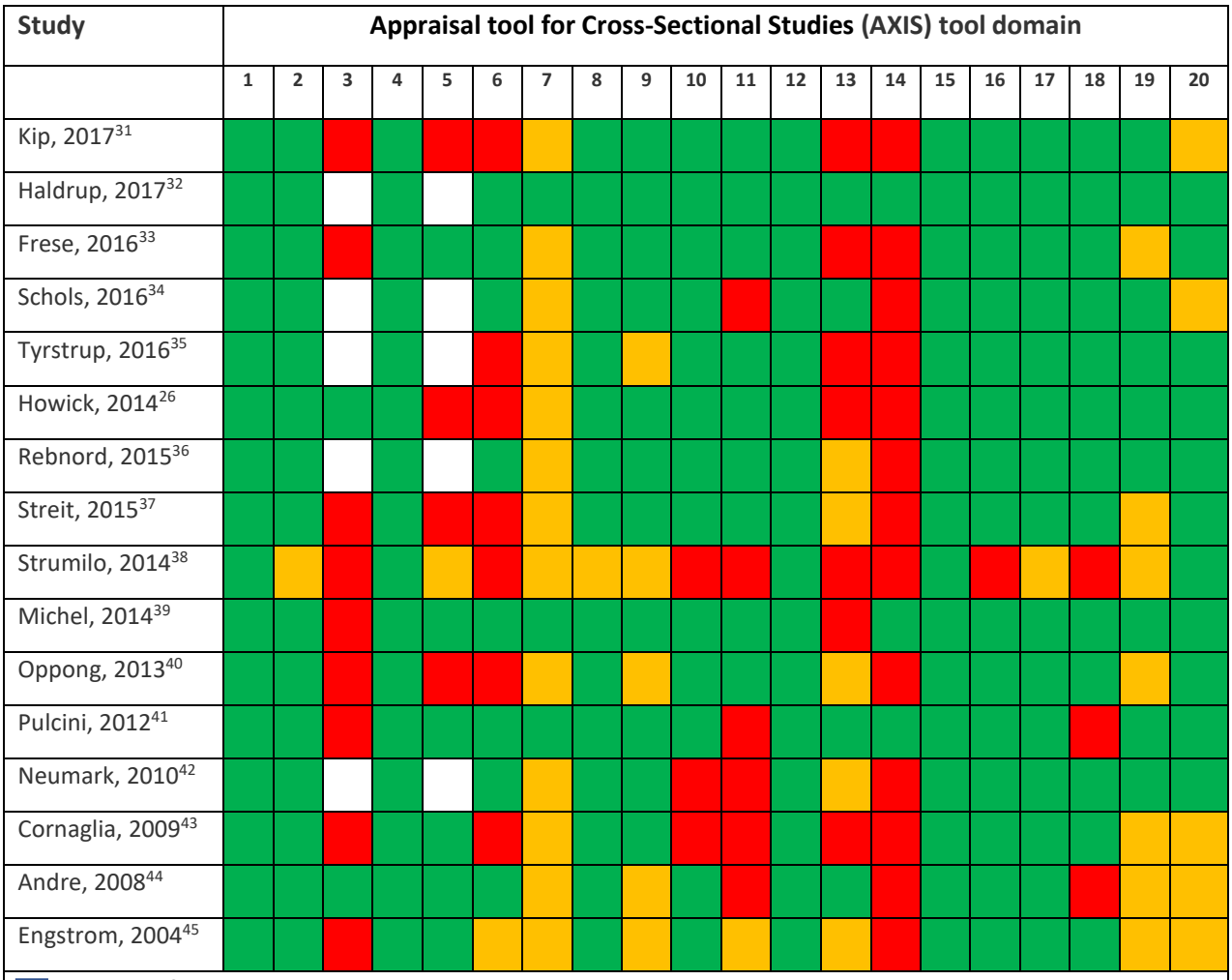
	consultations; 1999-2005		data from 240,445 consultations		respiratory infections					
Cornaglia, 2009[43]	Prospective cross-sectional assessment of GP consultations and data from social health insurance; 2005-2007	France; GP practices	Availability of GAS POCTs: social health insurance database. Use of GAS POCTs: Case records; 527 consultations with 66 different GPs	Local (Paris)	Children and adults with respiratory infections	GAS	Quantitative estimates	_	Quantitative estimates	Quantitative estimates
Andre, 2008[44]	Prospective cross-sectional assessment of GP consultations; 2005	Sweden; GP practices	Case records; 3,774 consultations from 135 GPs	Regional (5 counties)	Children and adults with a suspicion of infection	CRP, GAS	Anecdotical evidence	_	Quantitative estimates	_
Engstrom, 2004[45]	Retrospective cross-sectional assessment of consultations; 2001	Sweden; GP practices	Case records; 19,965 consultations from 12 GPs practices	Regional (Joonkoping, Kalmar, and Ostergotland counties)	Children and adults with respiratory infections	CRP, GAS	_	_	Quantitative estimates	_

POCTs: point-of-care tests, CRP: C-reactive protein; GAS: Group A streptococcus; UD: urine dipsticks; GPs: general practitioners

Quality of the included studies

Overall, the quality of the included studies was moderately good, as per the AXIS criteria (Figure 5).

Figure 5. Quality of the included studies



5	Was the sample frame taken from an appropriate population base so that it closely represented the target population?
6	Was the selection process likely to select subjects/participants that were representative of the target population?
7	Were measures undertaken to address and categorise non-responders?
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?
9	Were the variables measured correctly using instruments that had been trialled, piloted or published previously?
10	Is it clear what was used to determined statistical significance and/or precision estimates? (eg, p values, CIs)
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?
12	Were the basic data adequately described?
13	Does the response rate raise concerns about non-response bias?
14	If appropriate, was information about non-responders described?
15	Were the results internally consistent?
16	Were the results of the analyses described in the methods, presented?
17	Were the authors' discussions and conclusions justified by the results?
18	Were the limitations of the study discussed?
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?
20	Was ethical approval or the consent of the participants attained?

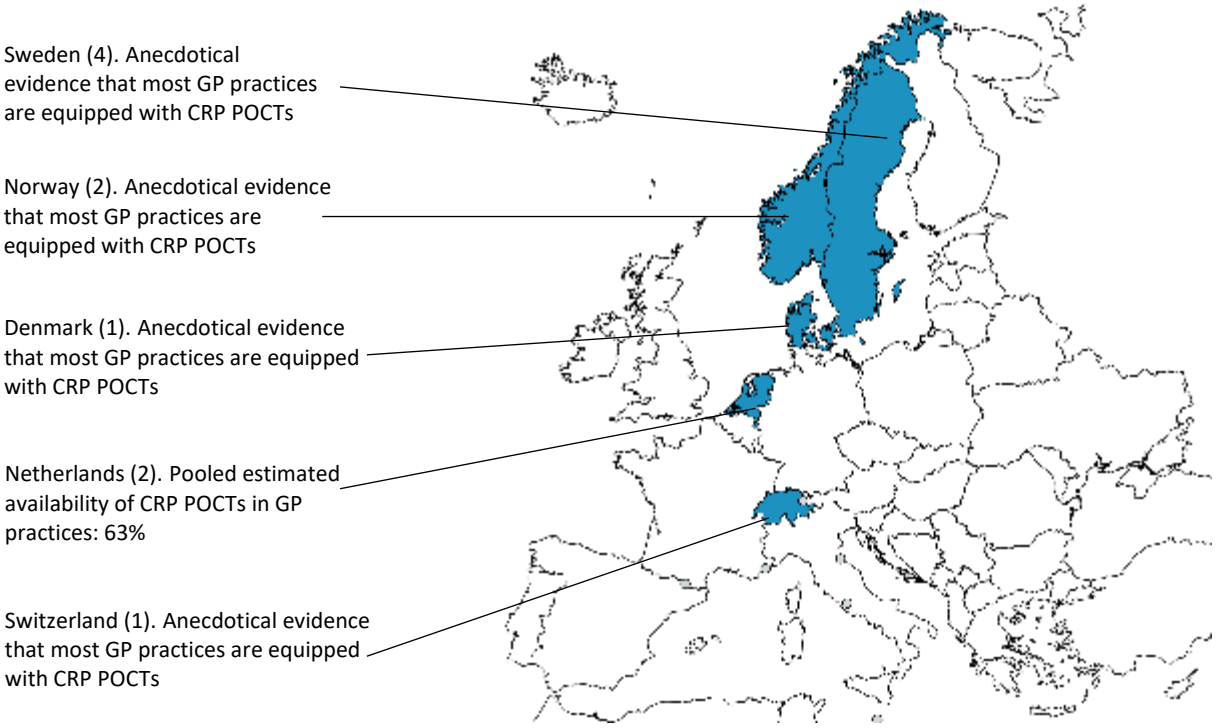
1.4.4.2. Estimates of the availability and use of CRP POCTs

Availability of CRP POCTs

Nine studies provided data on the availability of CRP POCTs in five countries: Denmark, the Netherlands, Norway, Sweden, and Switzerland (Figure 6).[31,32,34,35,36, 37,40, 42,44]

The studies from Denmark, Norway, Sweden, and Switzerland only provided anecdotical evidence in stating that CRP POCTs were available in most GP practices without providing quantitative data.

Figure 6. Availability of CRP POCTs in GP practices in European countries



The number of studies per country is shown in parentheses after the country name. CRP POCTs: C-reactive protein point-of-care tests, GP: general practitioner.

Two studies provided data on the availability of CRP POCTs in GP practices in the Netherlands.[31,34] The pooled estimated availability of CRP POCTs based on these two studies was 63% (95% CI: 57-69%) (Figure 7).

Use of CRP POCTs

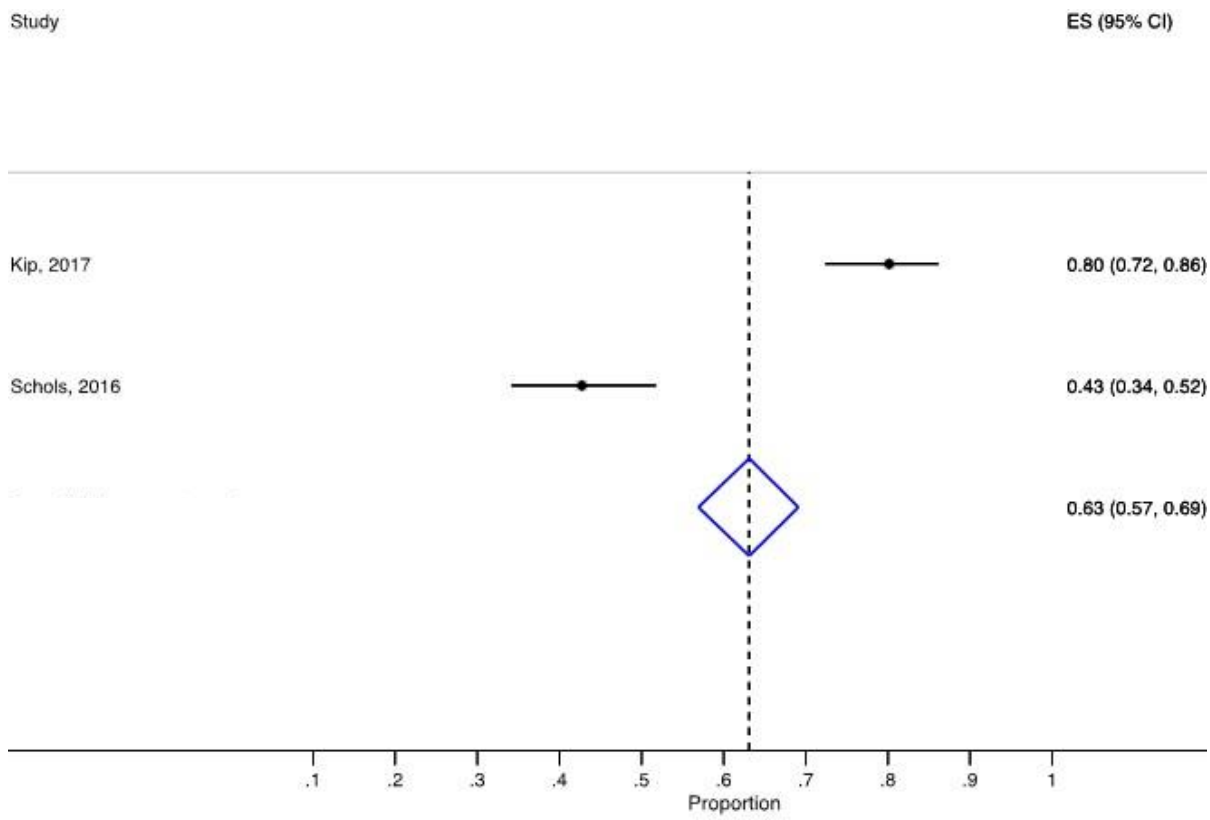
Eleven studies provided data on the use of CRP POCTs in 11 countries: Belgium, Denmark, Germany, Latvia, Lithuania, the Netherlands, Norway, Poland, Sweden, Switzerland, and the UK (Figure 8).[26,32,33,35,36,37,38,40,42,44,45]

One study provided data on the use of CRP POCTs by GPs in Belgium, the Netherlands, and the UK.[26] The study estimated that 3%, 48%, and 15% of GPs, respectively, used the tests without specifying the medical condition for which the tests were used.

One study estimated that Danish GPs used CRP POCTs in 7.1% of consultations in which antibiotics were prescribed.[32] In terms of use of the tests in children, CRP POCTS were used

in 7% of children aged 0-4 years, in 4% of children aged 5-9 years, and in 6% of children aged 15-19 years.

Figure 7. Availability of CRP POCTs in GP practices in the Netherlands



CRP POCTs: C-reactive protein point-of-care tests, GP: general practitioner.

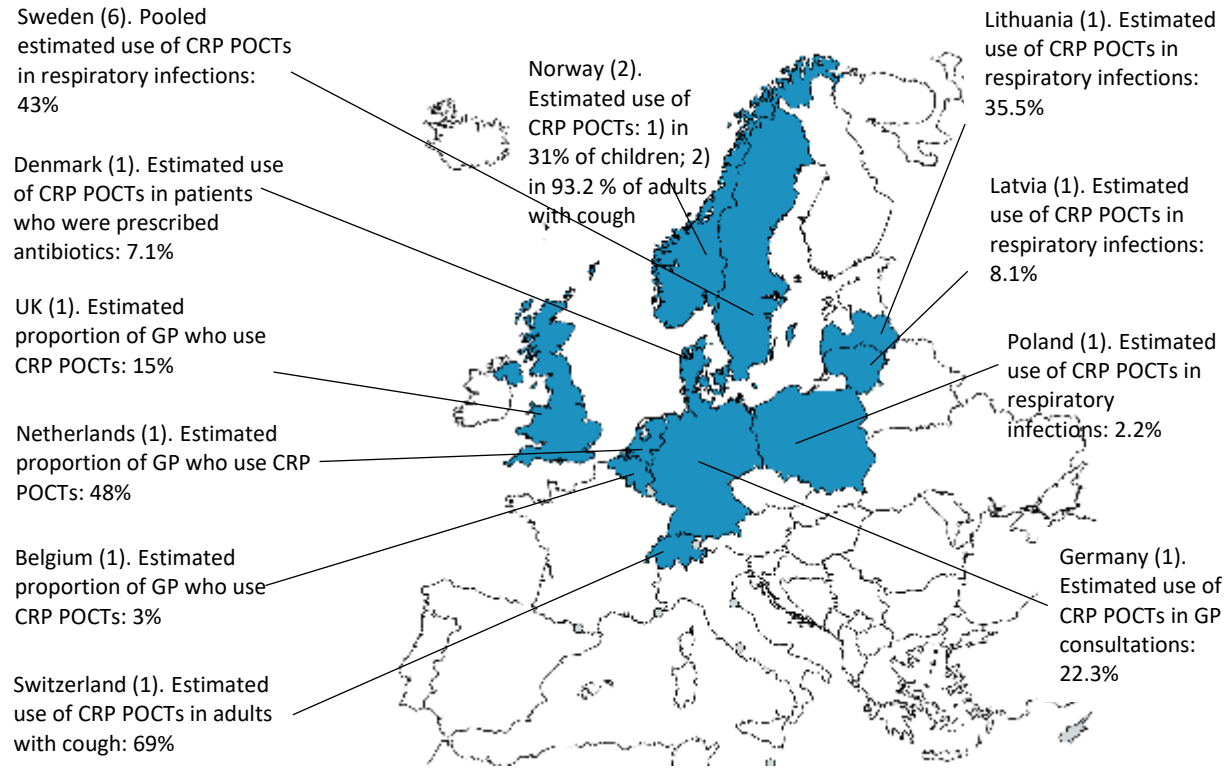
Another study provided data on the use of CRP POCTs by GPs in Germany.[33] The study estimated that 22.3 % of GPs used the tests in adults without specifying the medical condition for which the tests were used.

One study provided data on the use of CRP POCTs by GPs in Latvia, Lithuania, and Poland.[38] The study estimated that 8.1%, 35.5%, and 2.2% of GPs, respectively, used the tests in children and adults with respiratory infections.

Two studies provided data on the use of CRP POCTs in Norway.[36,40] Rebnord and colleagues estimated that CRP POCTs were used in 31 % of daytime consultations and in 44 % of consultations conducted out-of-hours in children, but without specifying the medical condition for which the tests were used. In terms of factors influencing the use of CRP POCTs, the study reported that doctors who were not GP specialists or had fewer children on their

patient lists were less likely to use CRP POCTs during the daytime (OR 0.7, 95%CI: 0.51-0.97, and OR 0.99, 95%CI: 0.98-0.99, respectively). GPs who were female were more likely to use CRP POCTs (OR 1.4, 95%CI: 1.02-2.0), as well as those who had a longer patient list (OR 1.1, 95%CI: 1.05-1.20) or a large number of consultations with children (OR 1.01, 95%CI:1.00-1.02). In out-of-hours, older doctors were less likely to use CRP POCTs (OR 0.96. 95%CI: 0.94-0.98), while GPs with a large number of consultations with children were more likely to use CRP POCTs (OR 1.03, 95%CI: 1.01-1.04). Oppong and colleagues estimated that CRP POCTs were used in 93.2% of consultations of adults with respiratory infections.

Figure 8. Use of CRP POCTs by GPs in European countries

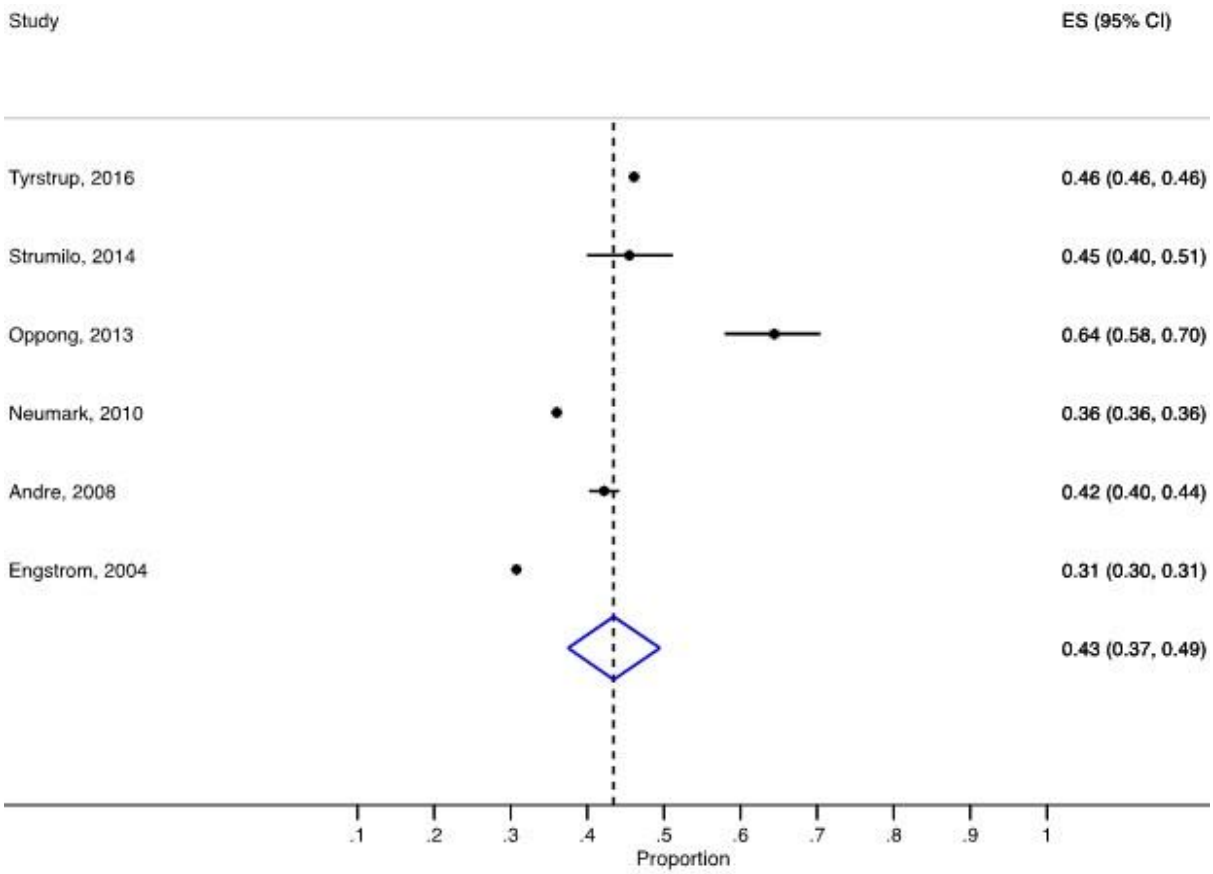


The number of studies per country is shown in parentheses after the country name. CRP POCTs: C-reactive protein point-of-care tests, GP: general practitioner.

Six studies provided data on the use of CRP POCTs in Sweden.[35,38,40,42,44,45] Among them, five studies[35,38,42,44,45] provided data about the use of CRP POCTs in adults and children with a respiratory infection; while one study provided data related to adults with a respiratory infection.[40] The pooled estimated use of CRP POCTs in patients with respiratory infections based on these six studies was 43% (95% CI: 37-49%) (Figure 9).

One study provided data on the use of CRP POCTs by GPs in Switzerland.[37] The study estimated that GPs used the tests in 69% cases of adults presenting with a cough.

Figure 9. Use of CRP POCTs in patients with respiratory infections by GPs in Sweden



CRP POCTs: C-reactive protein point-of-care tests, GP: general practitioner.

1.4.4.3. Estimates of the availability and use of GAS POCTs

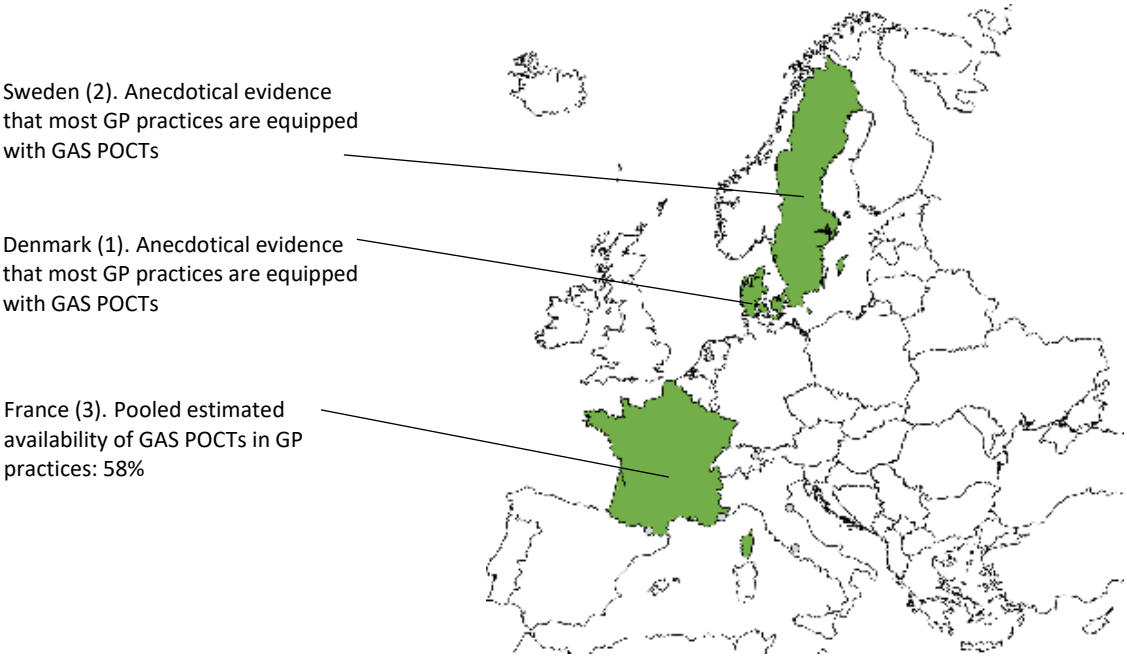
Availability of GAS POCTS

Six studies provided data on the availability of GAS POCTs in three countries: Denmark, France, and Sweden (Figure 10).[32,39,41,42,43,44]

The studies from Denmark and Sweden only provided anecdotical evidence in stating that GAS POCTs were available in most GP practices, without providing data. [32,42,44]

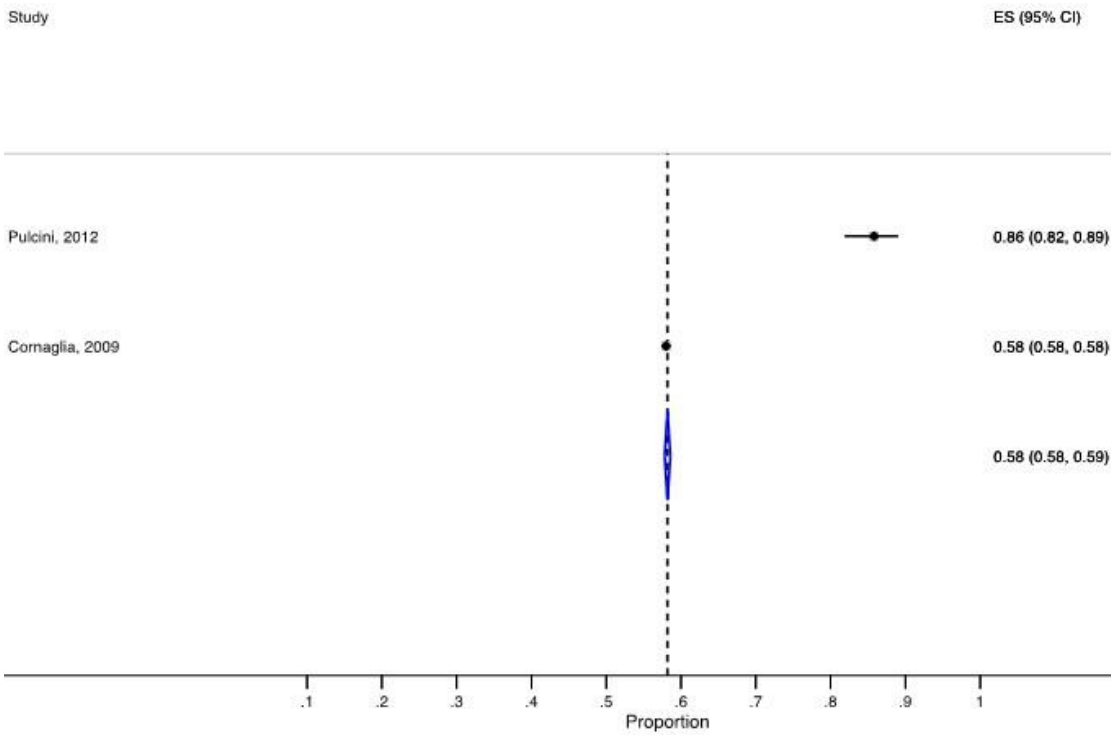
Two studies provided data on the availability of GAS POCTs in GP practices in France. The pooled estimated availability of GAS POCTs based on these three studies was 58% (95% CI: 58-59%) (Figure 11).[41,43]

Figure 10. Availability of GAS POCTs in GP practices in European countries



The number of studies per country is shown in parentheses after the country name. GAS POCTs: Group A streptococcus point-of-care tests, GP: general practitioner.

Figure 11. Availability of GAS POCTs in GP practices in France

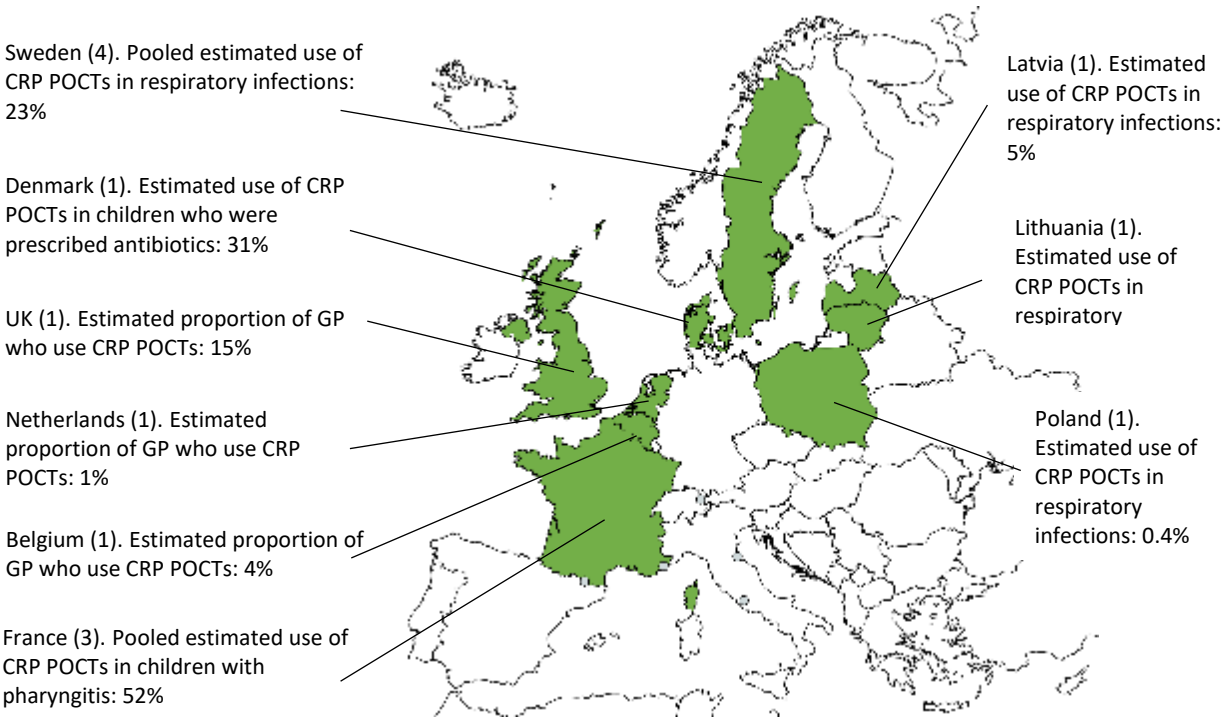


GAS POCTs: Group A streptococcus point-of-care tests, GP: general practitioner.

Use of GAS POCTs

Nine studies provided data on the use of GAS POCTs in nine countries: Belgium, Denmark, France, Latvia, Lithuania, the Netherlands, Poland, Sweden, and the UK (Figure 12).[26,32,38,39,41,42,43,44,45]

Figure 12. Use of GAS POCTs by GPs in European countries



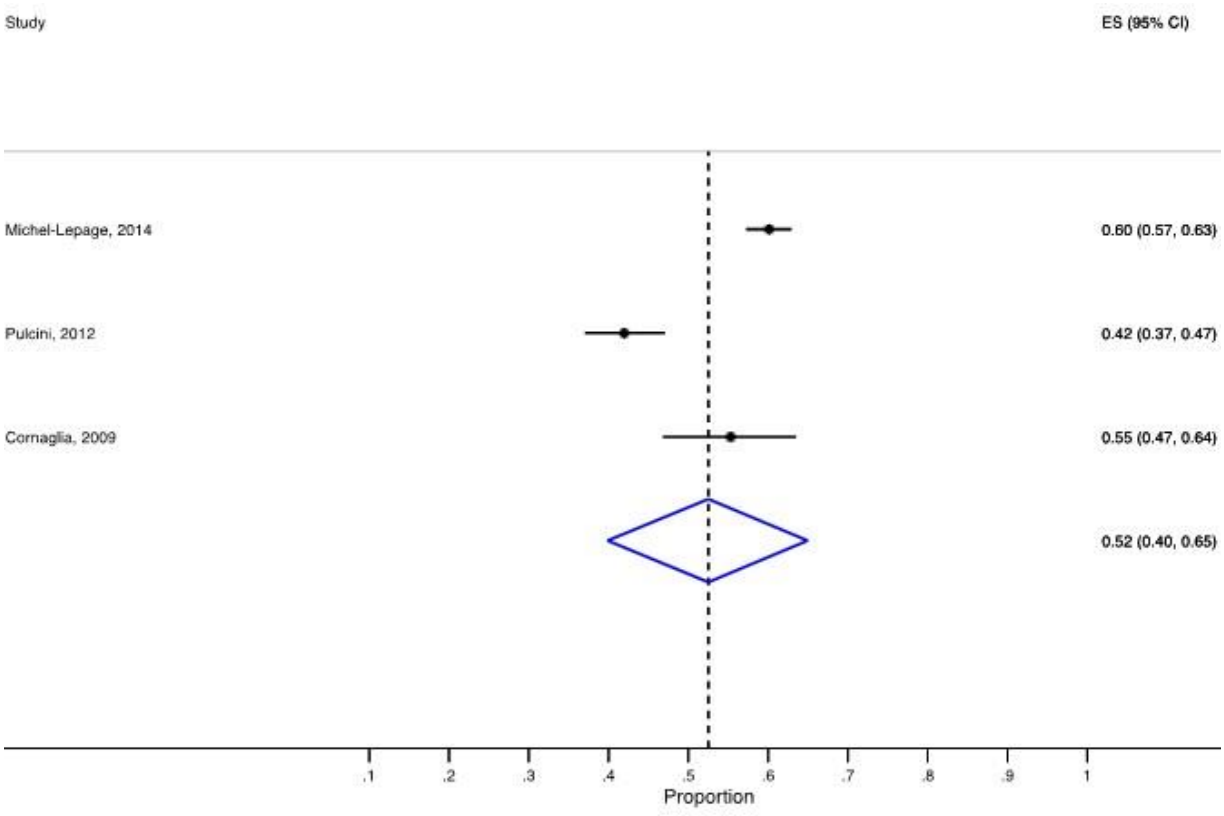
The number of studies per country is shown in parentheses after the country name. GAS POCTs: Group A streptococcus point-of-care tests, GP: general practitioner.

One study provided data on the use of GAS POCTs by GPs in Belgium, the Netherlands, and the UK. The study estimated that 4%, 1%, and 15% of GPs, respectively, used the tests for their patients.[26]

Another study estimated that Danish GPs used GAS POCTs in 3.4% of all consultations during which antibiotics were prescribed. In terms of the use of the tests in children, GAS POCTs were used in 19% of children aged 0-4 years, in 31% of children aged 5-9 years, and in 26% of children aged 15-19 years.[32]

The three studies from France provided data on the use of GAS POCTs in children with a sore throat. The pooled estimated availability of GAS POCTs based on the three studies was 52% (95% CI: 40-65%) (Figure 13).[39,41,43]

Figure 13. Use of GAS POCTs in children with respiratory infections by GPs in France



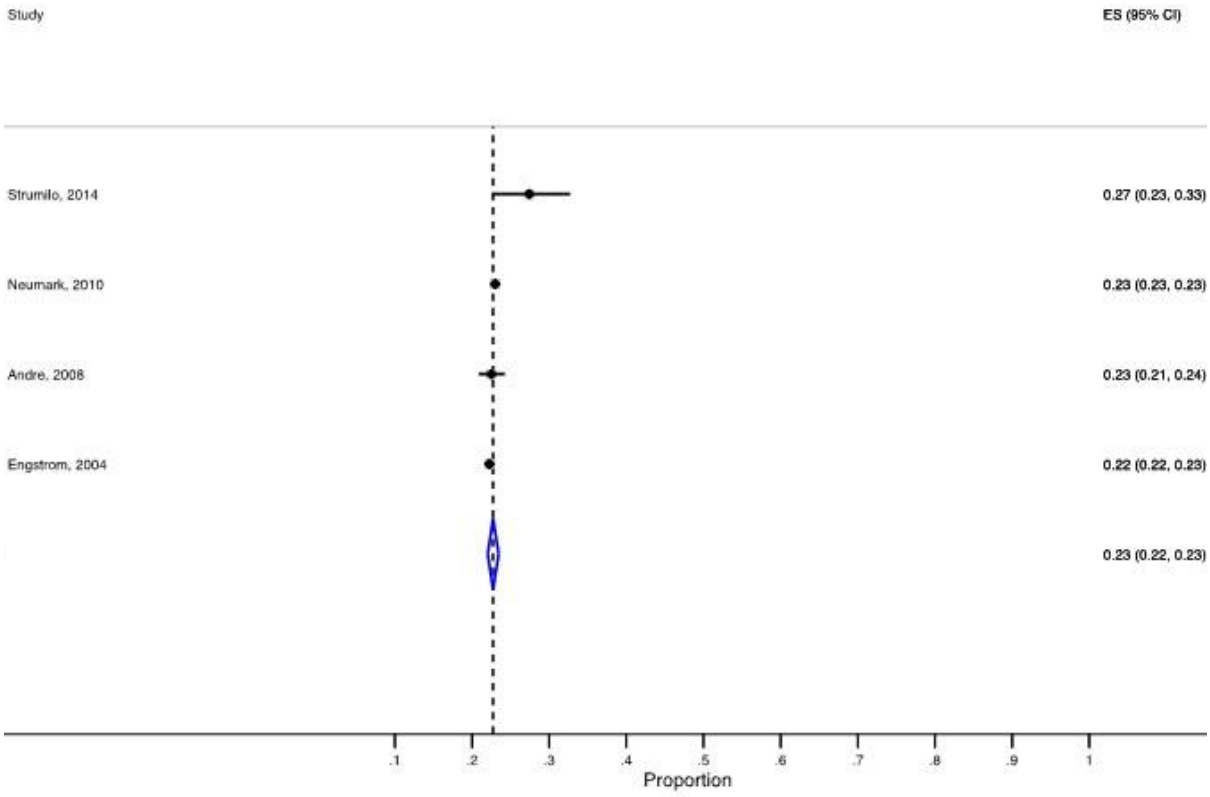
GAS POCTs: Group A streptococcus point-of-care tests, GP: general practitioner.

In terms of factors influencing the use of GAS POCTs, Michel-Lepage and colleagues found that GPs aged 45-54 years were more likely to use GAS POCTs (OR 1.13, 95%CI: 1.01-1.25), as well as those who attended continuous medical education programmes (OR 1.12, 95%CI: 1.03-1.21).[39] Pulcini and colleagues reported that the three main reasons cited by GPs for not using a GAS POCT were: 1) it takes too long (66.9% of GPs); 2) patients absolutely want antibiotics (62.7% of GPs); and 3) GAS POCTs are not needed because clinical signs are sufficient (51.5% of GPs).[41] Cornaglia and colleagues found that 59.2 % of GPs do not use GAS POCTs because they believe that clinical signs are sufficient to guide clinical management.[43]

One study provided data on the use of CRP POCTs by GPs in Latvia, Lithuania, and Poland. The study estimated that 5%, 2%, and 0.4% of GPs, respectively, used the tests in children and adults with respiratory infections.[38]

Four studies provided data on the use of GAS POCTs by GPs in children and adults with respiratory infections in Sweden. The pooled estimated use of GAS POCTs based on the four studies was 23% (95% CI: 22-23%) (Figure 14).[38,42,44,45]

Figure 14. Use of GAS POCTs in children and adults with respiratory infections by GPs in Sweden



GAS POCTs: Group A streptococcus point-of-care tests, GP: general practitioner

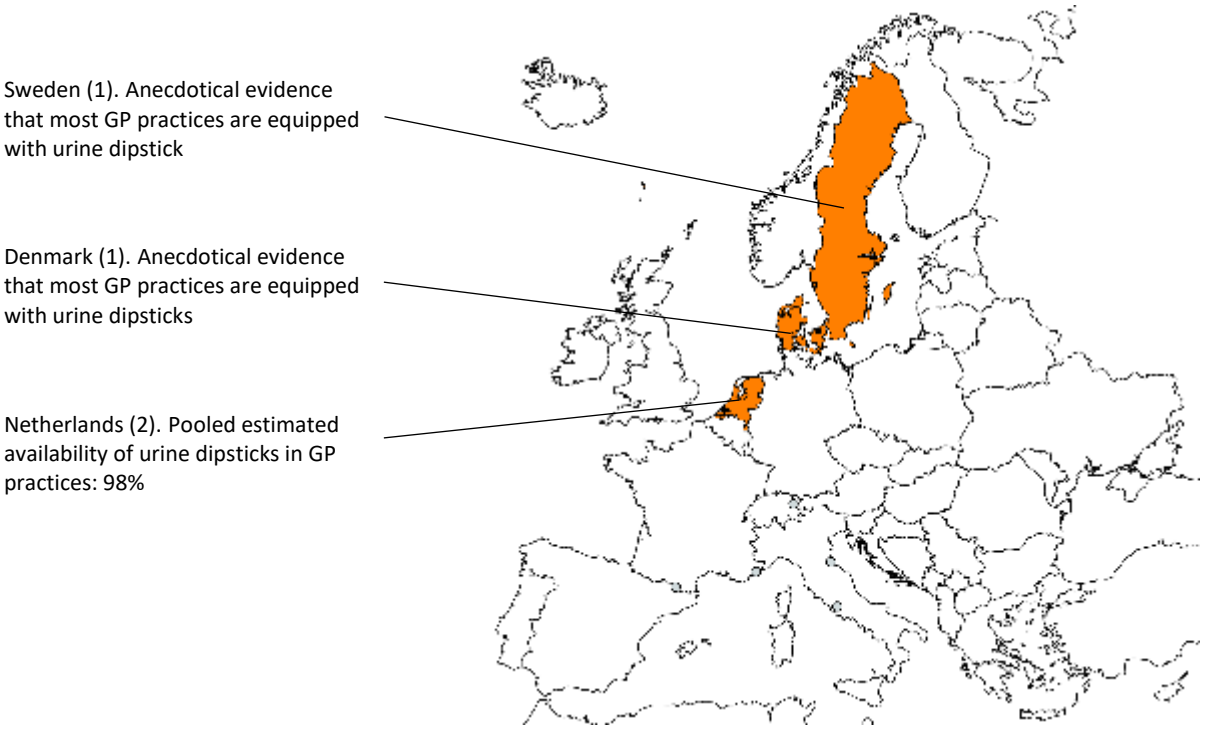
1.4.4.4. Estimates of the availability and use of urine dipsticks

Availability of urine dipsticks

Four studies provided data on the availability of urine dipsticks in three countries: Denmark, the Netherlands, and Sweden (Figure 15).[31,32,34,44]

The studies from Denmark and Sweden provided anecdotical evidence about the availability of urine dipsticks in GP practices in suggesting that the tests were available in most practices, but without providing specific data.[32,44]

Figure 15. Availability of urine dipsticks in GP practices in European countries



The number of studies per country is shown in parentheses after the country name. GP: general practitioner.

Two studies provided data on the availability of urine dipsticks in GP practices in the Netherlands. The pooled estimated availability of UDs bases on the two studies was 98% (95% CI: 96-100%) (Figure 16).[31,34]

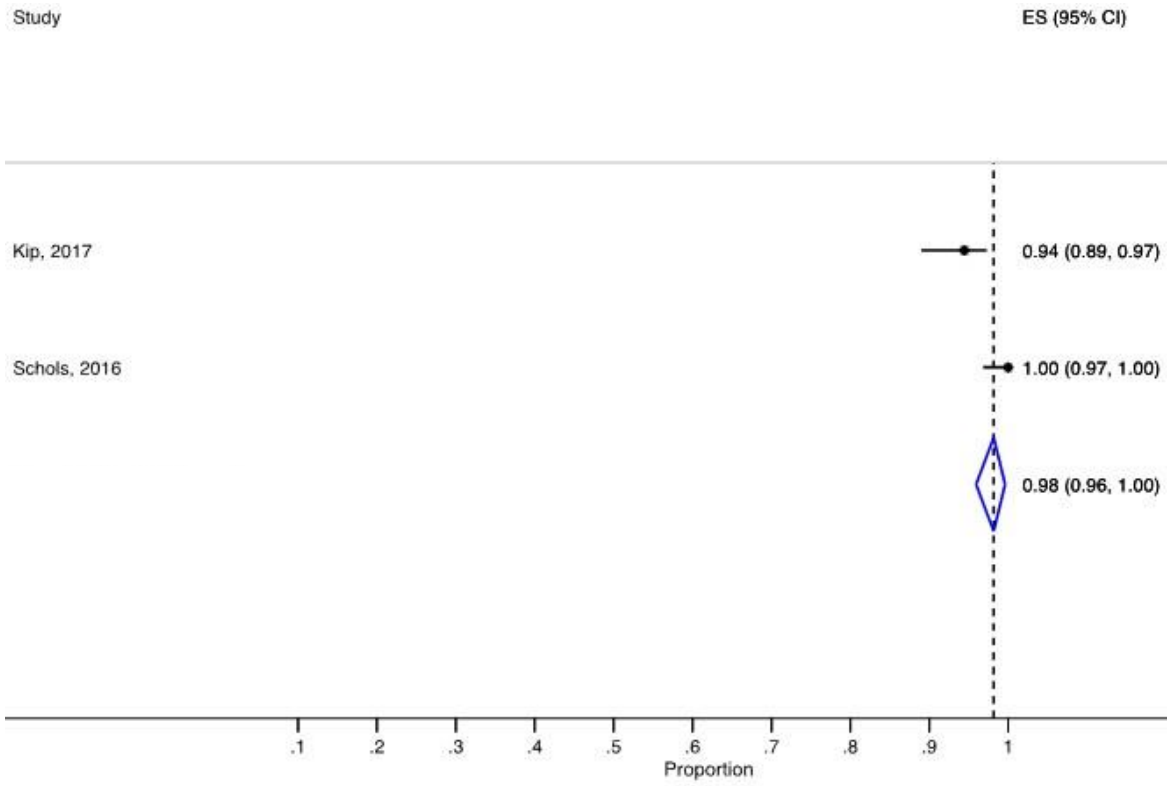
Use of urine dipsticks

Three studies provided data on the use of urine dipsticks in five countries: Belgium, Denmark, the Netherlands, Sweden, and the UK (Figure 17).[26,32,44]

One study provided data on the use of urine dipsticks by GPs in Belgium, the Netherlands, and the UK. The study estimated that 87%, 96%, and 97% of GPs, respectively, used the tests in their patients.[26]

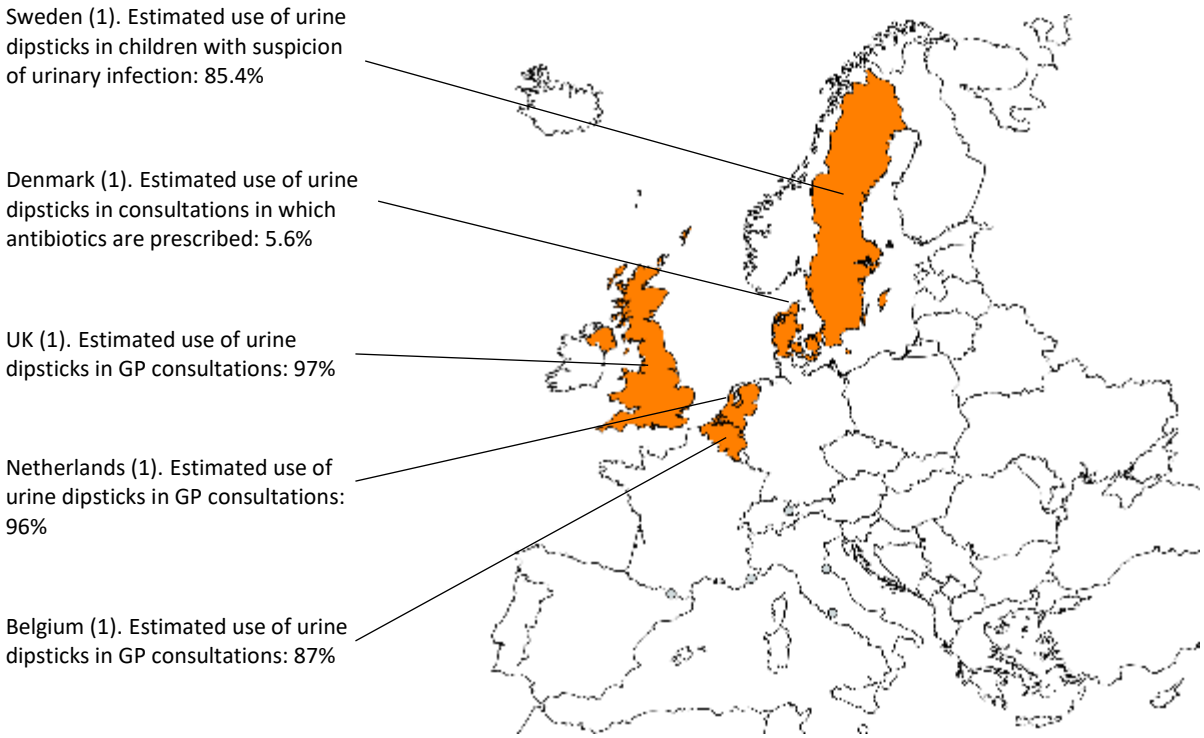
Another study estimated that Danish GPs used UDs in 5.6 % of all consultations in which antibiotics were prescribed. In terms of the use of the tests in children, urine dipsticks were used in 2% of children aged 0-4 years who were prescribed antibiotics, in 6% of children aged 5-9 years, and in 6% of children aged 15-19 years.[32]

Figure 16. Availability of urine dipsticks in GP practices in the Netherlands



GP: general practitioner.

Figure 17. Use of urine dipsticks by GPs in European countries



The number of studies per country is shown in parentheses after the country name. GP: general practitioner.

One study estimated that Swedish GPs used urine dipsticks in 85.4 % of consultations of children and adults with a suspicion of urinary tract infection.[44]

1.4.5. Discussion

1.4.5.1. Summary of main results

CRP POCTs are estimated to be available in 63% (95%CI: 57-69%) of GP practices in the Netherlands. The tests are reported to be available in most GP practices in Denmark, Norway, Sweden, and Switzerland, as well as in some practices in Belgium, Germany, Latvia, Lithuania, Poland, and the UK. The included studies did not provide information regarding the determinants of the availability of the tests.

The proportion of GPs who regularly use the tests varies substantially across the countries, from 3% of GPs in Belgium to 48% in the Netherlands. The main condition for which CRP POCTs are used is for respiratory infections. Here, again there are important variations across the surveyed countries: the estimates of CRP POCTs use vary from 2.2% of consultations for respiratory symptoms in Latvia to 93.2% in Norway, for example.

With regards to the use of CRP POCTs in children, only two studies (one from Denmark, the other from Norway) provided specific data on the use of the tests for this section of the population. CRP POCTs are used in less than 7% of children who were prescribed antibiotics in Denmark. In Norway, CRP POCTs were used in 31 % of children presented to GPs during the daytime and in 44 % of those seen out-of-hours. The latter study was the only one which examined the determinants of CRP POCTs use. Doctors who were not GP specialists or who had fewer children on their patient lists were less likely to use CRP POCTs during the daytime. Doctors who were female were more likely to use CRP POCTs, as well as those who had a longer patient list. During out-of-hours consultations, older doctors and doctors who had less children in their patient lists were less likely to use CRP POCTs.

The included studies did not provide any information regarding the availability and use of CRP POCTs in hospitals.

GAS POCTs are estimated to be available in 58% (95% CI: 58-59%) of GP practices in France. The tests are reported to be available in most GP practices in Denmark and Sweden, as well as in some practices in Belgium, Latvia, Lithuania, the Netherlands, Poland, and the UK. The included studies did not provide any information about the determinants of the availability of the tests.

The proportion of GPs who regularly use the tests, again, varies substantially across the countries, from 1% of GPs in the Netherlands to most GPs in Sweden. The proportion of patients with pharyngitis for which the tests are used also varies across the countries, from 0.4% of overall consultations (including children and adults) in Poland to 23% in Sweden.

With regards to the use of GAS POCTs in children, only two studies (one from Denmark, the other from France) provided specific data on the use of the tests for this section of the population. GAS POCTs were used in up to 31% of children who were prescribed antibiotics in Denmark. In France, GAS POCTs were used in 52% of children presenting with pharyngitis. The studies from France were the only studies to provide information on contributing factors or determinants of the use of GAS POCTs. One of the studies found that GPs aged 45-54 years and those who attended continuous medical education programmes were more likely to use GAS POCTs. The two other studies found that one of the main reasons GPs do not use the tests was that GAS POCTs are perceived as not useful when clinical signs are perceived as sufficient to guide the clinical management of patients.

The included studies did not provide data about the availability and use of GAS POCTs in hospitals.

Urine dipsticks are estimated to be available in 98% (95% CI: 96-100%) of GP practices in the Netherlands. The tests are available in most GP practices in Belgium, Denmark, the Netherlands, Sweden, and the UK. The included studies did not provide any information about the determinants of the availability of the tests.

The proportion of GPs who regularly use the tests was similar across the countries, from 85.4% of GPs in the Sweden to 97% in the UK. The included studies did not provide data about determinants of the use of the tests.

The included studies did not provide any information regarding the availability and use of urine dipsticks in hospitals.

1.4.5.2. Limitations

Only three POCTs were the focus of the identified studies. All the studies were conducted in a primary care setting, and no studies about the availability and use of POCTs in hospitals were identified. Most of the studies focused on the use of POCTs in adults, or adults and children without providing separated data on the use of POCTs in children. All the identified studies were from Northern European countries, particularly Scandinavian countries and, to a lesser extent, from France and the Netherlands.

1.4.5.3. Certainty of the evidence presented in this review

The certainty of the evidence presented in this review is limited by several factors. With regards to the availability of POCTs, several studies only provided anecdotical evidence without quantitative estimates. In some studies, the distinction between availability and use was unclear. There were no studies which investigated the determinants of the availability of POCTs. The few studies which explored the determinants of the use of POCTs only investigated the role of the doctors' characteristics (such as specialty, age, and gender), and no study examined the influence of factors such as health services or health systems factors on the availability and use of POCTs.

1.4.5.4. Agreements and disagreements with other studies or reviews

To the best of the PhD candidate's knowledge, there are currently no published systematic reviews about the availability and use of POCTs for the clinical management of acute infections in children in European countries. One report published by a company producing rapid diagnostic tests (Cooke, 2015)[46] reported that CRP POCTs were used widely in Denmark, Norway, Sweden, Germany, the Netherlands, and Switzerland, which is in keeping with the findings of this review. However, the report did not provide the source of its data, nor any quantitative estimates.

1.4.6. Conclusion

CRP POCTs are widely available in primary care practices in Scandinavian countries and the Netherlands. These tests are used mainly for the management of respiratory infections in adults, with substantial variation across the countries. GAS POCTs are widely available in primary care practices in Scandinavian countries and in France, and the extent of their use also varies across the countries. Urine dipsticks are widely available and used across Northern European countries.

The extent of the availability of these POCTs and other POCTs in hospitals and in other European countries is unclear, as well as the extent of the use of these and other POCTs in children. What the determinants of the availability and use of POCTs in the management of acute childhood infections are is unclear and, thus, warrants further investigations.

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1.6. Appendix: search strategy

1.6.1 Embase

Search	Term(s)	Results
1	exp adoption/	19234
2	(implementation or adoption or availability).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	770893
3	exp Point-of-Care Systems/	3141
4	(("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) adj2 (test* or analys*)).mp.	67233

	[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	
5	exp urine test strip/	1407
6	urine dipstick.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1554
7	exp Streptococcus group A/	8734
8	Streptococcus group A.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	9003
9	exp respiratory syncytial virus infection/	6559
10	(respiratory syncytial virus or RSV).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	29460
11	influenza.mp. or exp influenza/	183866
12	exp Calcitonin/	28904
13	(calcitonin* or procalcitonin* or pct).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	80311
14	exp C-Reactive Protein/	218174
15	("c reactive protein" or "c-reactive protein" or "C-reactive protein" or crp).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	267201
16	exp blood cell count/	366158
17	blood cell count.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	84581
18	blood gas.mp. or exp blood gas/	121858
19	lactate.mp. or lactic acid/	278835
20	exp Europe/	1826027
21	(Europ* or Austria or Belgium or Bulgaria or Croatia or Cyprus or Czech Republic or Denmark or Estonia or Finland or France or Germany or Greece or Hungary or Iceland or Ireland or Italy or Latvia or Lithuania or Luxembourg or Malta or Netherlands or Norway or Poland or Portugal or Romania or Slovakia or Slovenia or Spain or Sweden or Switzerland or United Kingdom or UK or Ukraine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,	3230876

	device trade name, keyword heading word, floating subheading word, candidate term word]	
22	1 or 2	770893
23	3 or 4	69647
24	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	1217775
25	20 or 21	3373391
26	22 and 23 and 24 and 25	158
27	**limit 26 to (human and yr="2002 - 2019")**	**102**

1.6.2 Medline

Search	Term(s)	Results
1	exp adoption/	4880
2	(implementation or adoption or availability).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	625121
3	exp Point-of-Care Systems/	18241
4	(("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) adj2 (test* or analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	37204
5	exp urine test strip/	0
6	urine dipstick.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	808
7	exp Streptococcus group A/	14061
8	Streptococcus group A.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	289
9	exp respiratory syncytial virus infection/	7968
10	(respiratory syncytial virus or RSV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	20308
11	influenza.mp. or exp influenza/	122239
12	exp Calcitonin/	16072
13	(calcitonin* or procalcitonin* or pct).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept	44227

	word, rare disease supplementary concept word, unique identifier, synonyms]	
14	exp C-Reactive Protein/	50778
15	("c reactive protein" or "c-reactive protein" or "C-reactive protein" or crp).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	107209
16	exp blood cell count/	149296
17	blood cell count.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	36778
18	blood gas.mp. or exp blood gas/	37389
19	lactate.mp. or lactic acid/	161677
20	exp Europe/	1514392
21	(Europ* or Austria or Belgium or Bulgaria or Croatia or Cyprus or Czech Republic or Denmark or Estonia or Finland or France or Germany or Greece or Hungary or Iceland or Ireland or Italy or Latvia or Lithuania or Luxembourg or Malta or Netherlands or Norway or Poland or Portugal or Romania or Slovakia or Slovenia or Spain or Sweden or Switzerland or United Kingdom or UK or Ukraine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1810079
22	1 or 2	625121
23	3 or 4	48586
24	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	640393
25	20 or 21	2043296
26	22 and 23 and 24 and 25	65
27	**limit 26 to (human and yr="2002 - 2019")**	**41**

1.6.3 Scopus

6	(TITLE-ABS-KEY (implementation OR adoption OR availability OR use)) AND (TITLE-ABS-KEY ("point of care" OR "point-of-care" OR "near patient" OR poc OR rapid OR bedside W/2 test* OR analys* OR diagnostic*)) AND (TITLE-ABS-KEY ("urine test strip" OR "urine dipstick" OR "streptococcus group a" OR "group a streptococcus" OR "respiratory syncytial virus" OR rsv OR influenza OR procalcitonin* OR pct OR "c reactive protein" OR "c-reactive protein" OR "c-reactive protein" OR cp OR "blood cell count" OR "blood gas analysis" OR lactate OR "lactic acid")) AND (TITLE-ABS-KEY (europ* OR austria OR belgium OR bulgaria OR croatia OR cyprus OR "czeh republic" OR denmark OR estonia OR finland OR france OR germany OR greece OR hungary OR iceland OR ireland OR italy OR latvia OR lithuania OR luxembourg OR malta OR netherlands OR norway OR poland OR portugal OR romania OR slovakia OR slovenia OR spain OR sweden OR switzerland OR "united kingdom" OR uk OR ukraine)) AND (LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2003)) Show less	63 results
5	(TITLE-ABS-KEY (implementation OR adoption OR availability OR use)) AND (TITLE-ABS-KEY ("point of care" OR "point-of-care" OR "near patient" OR poc OR rapid OR bedside W/2 test* OR analys* OR diagnostic*)) AND (TITLE-ABS-KEY ("urine test strip" OR "urine dipstick" OR "streptococcus group a" OR "group a streptococcus" OR "respiratory syncytial virus" OR rsv OR influenza OR procalcitonin* OR pct OR "c reactive protein" OR "c-reactive protein" OR "c-reactive protein" OR cp OR "blood cell count" OR "blood gas analysis" OR lactate OR "lactic acid")) AND (TITLE-ABS-KEY (europ* OR austria OR belgium OR bulgaria OR croatia OR cyprus OR "czeh republic" OR denmark OR estonia OR finland OR france OR germany OR greece OR hungary OR iceland OR ireland OR italy OR latvia OR lithuania OR luxembourg OR malta OR netherlands OR norway OR poland OR portugal OR romania OR slovakia OR slovenia OR spain OR sweden OR switzerland OR "united kingdom" OR uk OR ukraine)) Show less	93 results
4	TITLE-ABS-KEY (europ* OR austria OR belgium OR bulgaria OR croatia OR cyprus OR "czeh republic" OR denmark OR estonia OR finland OR france OR germany OR greece OR hungary OR iceland OR ireland OR italy OR latvia OR lithuania OR luxembourg OR malta OR netherlands OR norway OR poland OR portugal OR romania OR slovakia OR slovenia OR spain OR sweden OR switzerland OR "united kingdom" OR uk OR ukraine) Show less	5,012,950 results
3	TITLE-ABS-KEY ("urine test strip" OR "urine dipstick" OR "streptococcus group a" OR "group a streptococcus" OR "respiratory syncytial virus" OR rsv OR influenza OR procalcitonin* OR pct OR "c reactive protein" OR "c-reactive protein" OR "c-reactive protein" OR cp OR "blood cell count" OR "blood gas analysis" OR lactate OR "lactic acid") Show less	1,045,947 results
2	TITLE-ABS-KEY ("point of care" OR "point-of-care" OR "near patient" OR poc OR rapid OR bedside W/2 test* OR analys* OR	90,671 results
1	TITLE-ABS-KEY (implementation OR adoption OR availability OR use)	2,444,371 results

1.6.4 CINAHL Plus

#	Query	Limiters/Expanders	Last Run Via	Results
S15	S1 AND S2 AND S12 AND S13	Limiters - Published Date: 20020101-20191231; Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	51
S14	S1 AND S2 AND S12 AND S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	66
S13	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	98,429
S12	Europ* or Austria or Belgium or Bulgaria or Croatia or Cyprus or "Czech Republic" or Denmark or Estonia or Finland or France or Germany or Greece or Hungary or Iceland or Ireland or Italy or Latvia or Lithuania or Luxembourg or Malta or Netherlands or Norway or Poland or Portugal or Romania or Slovakia or	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	681,858

	Slovenia or Spain or Sweden or Switzerland or "United Kingdom" or UK or Ukraine			
S11	lactate or "lactic acid"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	18,699
S10	blood gas analysis	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	5,768
S9	"blood cell count"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	6,016
S8	"c reactive protein" or "c-reactive protein" or "C-reactive protein" or crp	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	31,000
S7	procalcitonin* or pct	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	4,713
S6	influenza	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	32,449

			Database - CINAHL Complete	
S5	"respiratory syncytial virus" or RSV	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	3,498
S4	"Streptococcus group A" or "group A Streptococcus"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	530
S3	"urine test strip" or "urine dipstick"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	272
S2	("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) W2 (test* or analys* or diagnostic*)	Limiters - Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	30,112
S1	implementation or adoption or availability or use	Limiters - Human; Geographic Subset: Europe Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	266,628

1.6.5 Web of Science

☐	6	#3 AND #2 AND #1 AND #5	384
☐	5	ALL=(europ* OR austria OR belgium OR bulgaria OR croatia OR cyprus OR "Czeh Republic" OR denmark OR estonia OR finland OR france OR germany OR greece OR hungary OR iceland OR ireland OR italy OR latvia OR lithuania OR luxembourg OR malta OR netherlands OR norway OR poland OR portugal OR romania OR slovakia OR slovenia OR spain OR sweden OR switzerland OR "United Kingdom" OR uk OR	22,591,459
☐	4	ALL=("urine test strip" OR "urine dipstick" OR "Streptococcus group A" OR "group A Streptococcus" OR "respiratory syncytial virus" OR rsv OR influenza OR procalcitonin* OR pct OR "c reactive protein" OR "c-reactive protein" OR "C-reactive protein" OR crp OR "blood cell count" OR "blood gas analysis" OR lactate OR "lactic acid")	555,055
☐	3	ALL=("urine test strip" OR "urine dipstick" OR "Streptococcus group A" OR "group A Streptococcus" OR "respiratory syncytial virus" OR rsv OR influenza OR procalcitonin* OR pct OR "c reactive protein" OR "c-reactive protein" OR "C-reactive protein" OR crp OR "blood cell count" OR "blood gas analysis" OR lactate OR "lactic acid")	555,055
☐	2	ALL=("point of care test*" OR "point-of-care test*" OR "near patient test*" OR poct OR "rapid test*" OR "bedside test*")	17,136
☐	1	implementation OR adoption OR availability OR use (Topic)	22,911,821

Chapter 2. Aim and objectives

2.1. Rationale

The adoption (i.e., the availability and use) of POCTs in the clinical management of infections has been widely advocated to improve the use of antibiotics and medical resources in general. The extent of the adoption of POCTs for the clinical management of acute childhood infections in European countries is unclear and seems to vary across countries.

C-Reactive protein (CRP) is one of the most extensively studied biomarkers for the management of infections. CRP POCTs seem to be widely available in primary care settings in some Northern European countries, but little is known about the extent of their use for diagnosing children. The availability and use of CRP POCTs in hospitals in European countries is largely undocumented.

Understanding the factors that contribute to the adoption of POCTs is important for informing the implementation of current and future POCTs, which data that is currently lacking.

2.2. Aim

The aim of this thesis is to address evidence gaps about the factors which contribute to the adoption of POCTs for the clinical management of acute childhood infections in European settings.

2.3. Objectives

The objectives of this thesis are:

- *Objective 1*: To estimate the variability in the availability and use of POCTs for the clinical management of acute childhood infections across European countries.

- *Objective 2:* To explore the determinants of this variability across European countries.

- *Objective 3:* To generate an in-depth understanding of the factors that contribute to high- versus low-level availability of CRP POCTs in primary care settings in two countries with similar primary healthcare systems, and to explore whether the tests are used in children.

- *Objective 4*: To generate an in-depth understanding of the factors that contribute to the different levels of availability and use of CRP POCTs in hospitals in these two countries.

Table 2 summarises current evidence gaps and the objectives of this thesis which aim to address these gaps.

Table 2. Evidence gaps and PhD objectives

Evidence gaps	PhD Objectives
The availability and use of POCTs for the clinical management of acute childhood infections in European countries seems to vary across countries, but current estimates for most countries are not available.	1.To estimate the variability in the availability and use of POCTs for the clinical management of acute childhood infections across European countries.
The determinants of this potential variability are unclear.	2. To explore the determinants of this variability across European countries.
CRP is one of the most used and studied biomarkers for the management of acute infections. Its availability varies across countries, and little is known about the factors that contribute to the availability and use of CRP POCTs in children in primary care.	3. To generate an in-depth understanding of the factors that contribute to high- versus low-level availability of CRP POCTs in primary care settings in two countries with similar primary healthcare systems, and to explore whether the tests are used in children.
The availability of CRP POCTs in hospitals also seems to vary across Europe. The factors that contribute to the availability and use of CRP POCTs in children in hospitals might be different to those at play in primary care and are unknown.	4. To generate an in-depth understanding of the factors that contribute to the different levels of availability and use of CRP POCTs in hospitals in these two countries.

CRP POCTs: C-reactive protein point-of-care tests

Chapter 3. Methods

This section provides an overview of the methods used in this thesis. It introduces the thesis' overarching methodological approach, as well as how the methods of the three studies that make up the thesis are combined and address the overall aim and objectives. More details about the methods of each study are provided in the studies' corresponding sections.

3.1. Conceptual framework

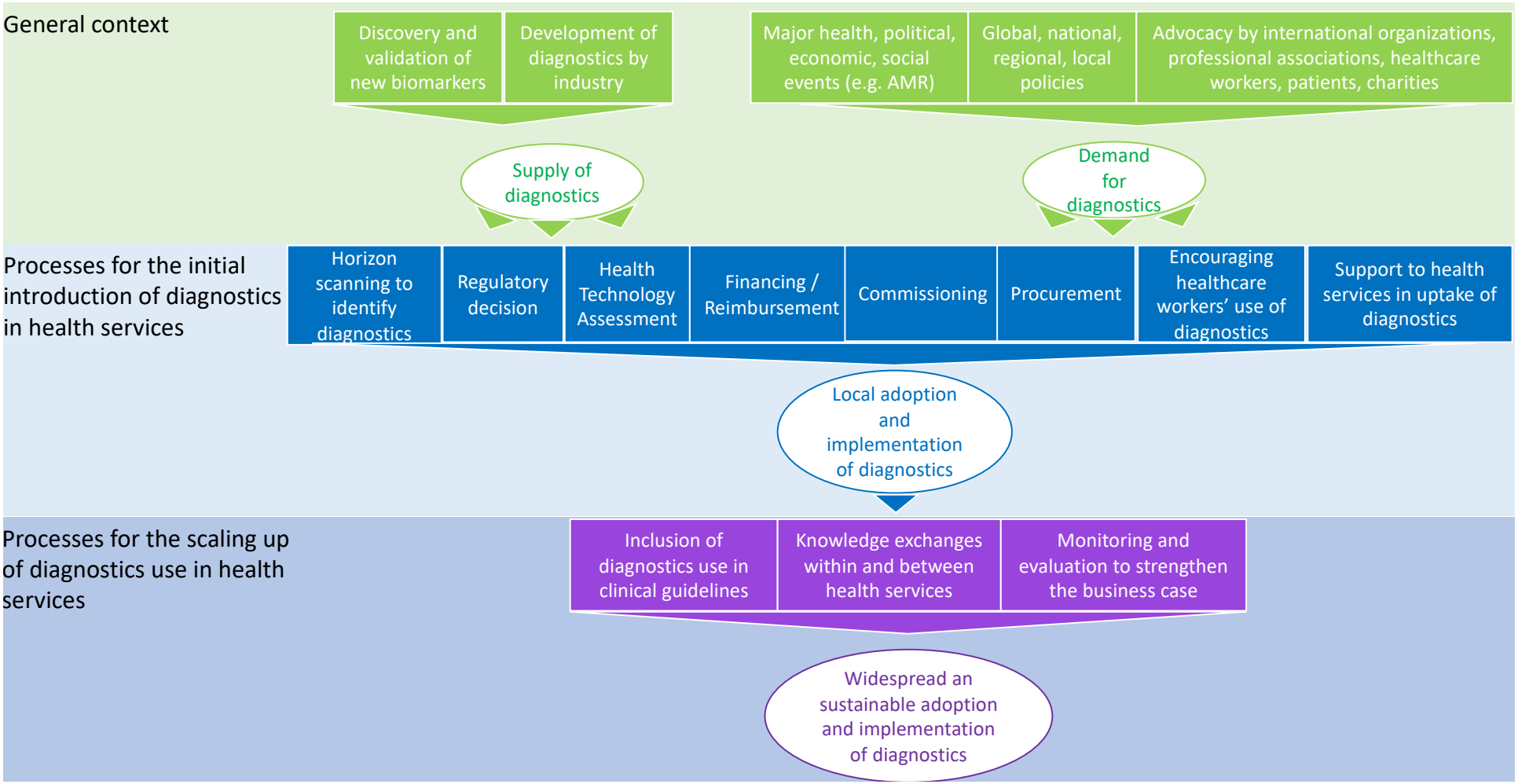
The adoption of innovations in health services is a multifaceted process involving multiple actors acting at different levels of the health systems. Thus, an examination of the whole health system is needed to understand the factors that contribute to the adoption of POCTs. Such an examinations should therefore include the tree levels of health systems:[1]

- The macro-level which is comprised of the policy, governance, and financing infrastructure and processes.
- The meso-level, which consists of the organisational level of the institutions which deliver healthcare (e.g., primary care practices or hospitals).
- The micro-level, which is focused on the process of healthcare delivery to patients and how healthcare providers and patients experience it.

Moreover, the adoption of innovations happens in a specific general country context.[2] The role of context in shaping the provision of healthcare is gaining recognition.[3] Understanding the mechanisms that enable adoption, while also considering the complexity of the context can be examined through a 'systems thinking' approach.[4] This approach treats health systems as a system made up of a series of sub-systems within each of the aforementioned three levels of health systems. This includes sub-systems for designing policies, identifying funds, distributing them to healthcare services, or for administering health services or parts of health services. Facilitators of and barriers to any of these sub-systems can have important consequences on the final shape of the system and, as is being examined in this thesis, on the adoption of POCTs. Importantly, a 'systems thinking' approach also aims to understand how subsystems, contexts, and actors act, react, and interact with each other.

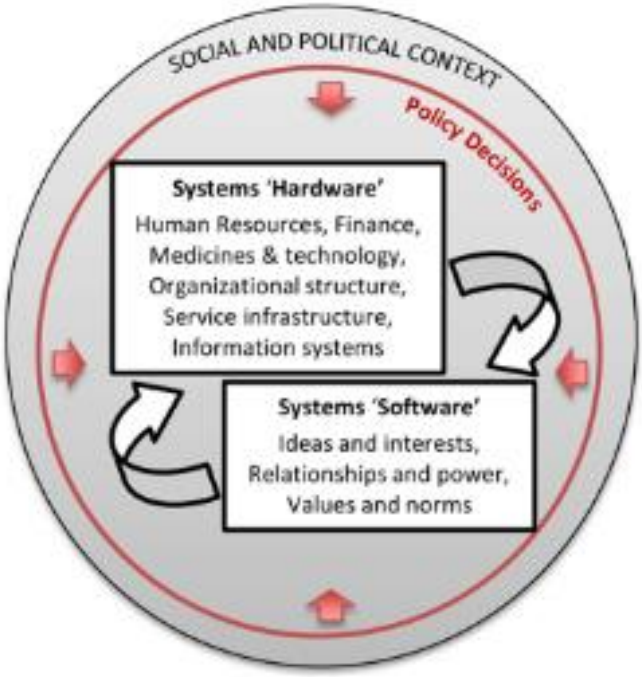
Based on these principles, the PhD candidate developed an initial framework informed by a scoping review of the literature to inform the design of the studies (Figure 18).

Figure 18. The PhD candidate's initial framework to assess the processes for the adoption of diagnostic tests in health services



However, the PhD candidate felt that the framework was too 'Donabedian',[5] i.e., too focussed on structures and processes, and did not sufficiently allow for the adopters' values, views, and social interactions to be incorporated in the analysis. Thus, the PhD candidate decided to use the existing 'hardware/software framework' framework, instead (Figure 19).[6]

Figure 19. The hardware/software health systems framework



Adapted from Sheikh, 2011[6]

The 'hardware' component of this framework relates to the infrastructure and processes of the sub-systems that enable the delivery of health services and are overall include in the PD candidate's framework. The 'software' component takes into account the fact that these infrastructures and processes are highly influenced by ideas, power dynamics, values, and norms of the actors of each subsystem. Lastly, the overall framework acknowledges the fact that the hardware and software components take place within a broader socio-economic and political context.

The advantage of an approach that focusses only on the broad levels of health systems or on a Donabedian framework is that it is simpler to carry out compared to using the approach suggested by the 'hardware/software' framework. However, by including ideas, power dynamics, values, and norms the 'hardware/software' framework allows a more in-depth

and comprehensive examination of the phenomenon of interest, which was needed to address the aim of his thesis.

3.2. Study designs

This thesis is based on a mixed-methods approach which combines quantitative and qualitative methods.[7] This approach was selected because both type of methods were needed: quantitative methods to estimate the extent of the availability and use of POCTs, in addition to identifying broader determinants across several European countries, and qualitative methods to gain an in-depth insight into the factors that contribute to the outcomes in very specific contexts (i.e., the Netherlands and England) and to provide a fuller picture of the phenomenon of interest. The quantitative and qualitative studies were conducted parallel to one another.

3.2.1. Quantitative methods

The quantitative component consisted of an online cross-sectional survey of primary care and hospital paediatricians from across Europe, which aims to address Objectives 1 and 2 (Figure 20).

Figure 20. Research design of the thesis and contribution of each study.

Aim of the PhD:
To address evidence gaps about the factors which contribute to the adoption of POCTs for the clinical management of acute childhood infections in European settings.

Approach	Objectives and methods	Source of data (in black) and contribution to thesis (in red)
Quantitative	**Objective 1:** To estimate the variability in the availability and use of POCTs for the clinical management of acute childhood infections across European countries. **Methods**: Cross-sectional online survey of European paediatricians	**Breadth** ↔ **Study 1**: 1154 Primary care paediatricians from 19 countries and 1188 Hospital-based paediatricians from 29 countries

	Objective 2: To explore the determinants of this variability across European countries. **Methods**: Multilevel logistic regressions.		
Qualitative	**Objective 3:** To generate an in-depth understanding of the factors that contribute to high- versus low-level availability of CRP POCTs in primary care settings in two countries with similar primary healthcare systems, and to explore whether the tests are used in children. **Methods:** Comparative qualitative case-studies based on a document review and in-depth interviews with stakeholders in the Netherlands and England.		**Study 2**: 65 documents and 21 qualitative interviews* from the Netherlands and England **Depth** **Study 3:** 41 documents and 46 qualitative interviews* from the Netherlands and England
	Objective 4: To generate an in-depth understanding of the factors that contribute to the different levels of availability and use of CRP POCTs in hospitals in these two countries. **Methods:** Comparative qualitative case-studies based on a document review and in-depth interviews with stakeholders in the Netherlands and England.		

**Thirteen documents and five interviews provided data pertaining to both primary settings care and hospitals and were therefore used in the two qualitative studies. The other documents and interviews were used only in one of the two studies.*

The cross-sectional survey intended to include as many European countries as possible to ensure breadth in terms of the estimates of the availability and use of POCTs. This was possible thanks to the dissemination of the survey through several pan-European and

national professional societies of paediatrics, which enabled the collecting of primary data from across Europe. The study focuses on the nine POCTs that were included in the literature review in the introduction section (see Chapter 1).

The study provides estimates about the availability and use of rapid diagnostic tests, as well as about the contribution of country, workplace and participants' characteristics on the availability and use of the tests (see analysis section below for further details). Thus, this study predominantly contributes to the aim of understanding the 'hardware' of the 'hardware/software' systems thinking approach.

3.2.2. Qualitative methods

The qualitative component consists of in-depth qualitative cases-studies that aim to address Objectives 3 and 4 (Figure 20). In contrast to the cross-sectional survey, the qualitative studies aimed to provide greater insight into the mechanisms that allow, or prevent, the adoption of POCTs, by focusing on two countries and one specific POCT. CRP POCTs were selected because CRP is one of the most used and studied biomarkers for the management of infections, as mentioned earlier. The Netherlands and England were selected because while the adoption of CRP POCTs is substantially greater in the Netherlands than in England, the countries share several characteristics:

1. General practitioners provide primary care to children and are the gate keepers of health services. Focusing on these two countries allowed the scope of the thesis to be extended to include GPs, who were not included in the cross-sectional survey but are important providers of healthcare to children in several European countries.
2. The majority (~80%) of the health expenditure in both countries is covered by public sector sources (primarily from compulsory social health insurance in the Netherlands, and from general taxation in England).[8]
3. Both countries are wealthy European countries which invest significant amounts of their wealth (~10 % of GDP) into healthcare.[9]

The two countries were also selected because the PhD candidate has colleagues in these two countries who were then able to support the implementation of the studies. A historical case-study design was used because it allows for an examination of the interactions between

the phenomenon of interest and the context in which it occurs, and for comparisons to be made between these cases.[10] In this thesis, each case is the sum of events that led to the adoption, or non-adoption, of CRP POCTs in primary care or hospitals in the two included countries.

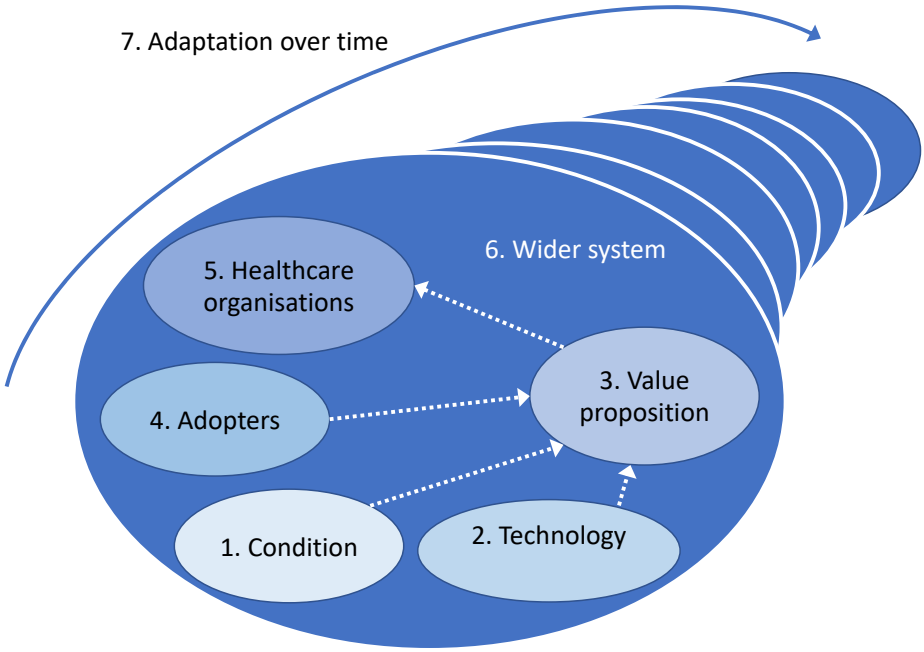
The design of the case-studies was informed by the existing non-adoption, abandonment, scale-up, spread and sustainability (NASSS) framework instead.[11] The NASSS framework was developed by Greenhalgh and colleagues in order to study the adoption of digital health technologies by assessing the complexity of seven domains: (1) the condition or illness; (2) the technology; (3) the value of the innovation for developers and users; (4) the adopters and whether the innovation implied a change in their role, identity, and practices; (5) the organisations where the innovation is implemented, their readiness for this innovation, how the innovation changes the organisations' routines, and the work needed to adopt, fund, and normalise the innovation; (6) the wider context including the policy and regulatory contexts, the role of professional bodies and interorganisational networking; and (7) the adaptation of the innovation, its use, and the organisations over time (Figure 21). There are several frameworks that can be used to examine the adoption of innovations, such as the diffusion of innovations theory or the normalisation process theory.[12,13] However, those frameworks are broad in scope, i.e., they were developed to examine the adoption of innovations in other fields than healthcare or for any type of intervention, while the NASSS framework presents the advantage of having been specifically developed for the adoption of technologies in healthcare services. Given that diagnostics are technologies, the NASSS frameworks was considered to be the most appropriate framework to address the objectives of the case-studies.

The source of data for the case-studies were documents and qualitative in-depth interviews. The documents pertained to the adoption of CRP POCTs and diagnostic tests in general in the Netherlands and England and were available in the public domain. The qualitative interviews were conducted with stakeholders who were experts in at least one domain of the NASSS framework pertaining to the adoption of CRP POCTs and/or diagnostic tests in the two countries.

The qualitative case-studies contribute to the aim of gaining a better understanding of the different aspects of 'hardware/software' systems thinking approach. Domains 2, 4, and 5 of

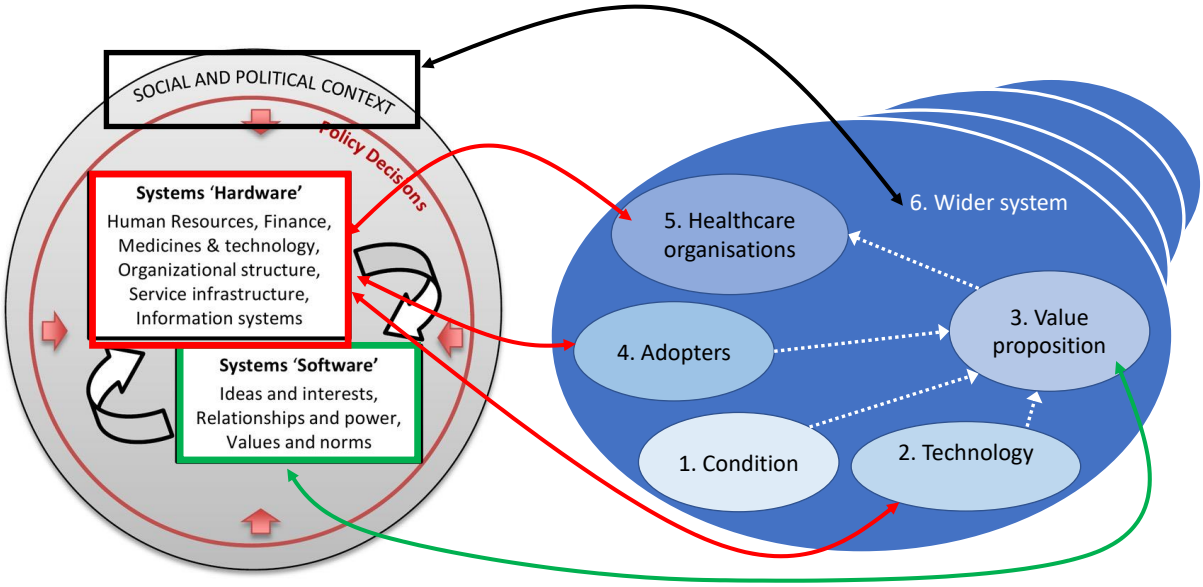
the NASSS framework contribute mainly (but not exclusively) to understanding the 'hardware'; domain 3 mainly contributes to the 'software', and domain 6 mainly contributes to the broader policy and socio-political context (Figure 22).

Figure 21. The non-adoption, abandonment, spread, scale-up and sustainability of healthcare technologies (NASSS) framework



Adapted from Greenhalgh et al, 2017[11]

Figure 22. Links between the NASSS and 'Hardware/software' frameworks



3.3. Analysis

The data were analysed iteratively, and the early results from the three studies were used to inform the refinement of the design and the analysis of the other studies, as the studies were conducted parallel to one another.

3.3.1. Quantitative analysis

Descriptive statistics were used to define the characteristics of the paediatricians and workplaces (primary care practices or hospitals) studied and to derive estimates of the availability and use of POCTs per country.

Multilevel logistic regressions were used to separately assess the impact of the different levels of the health systems on the availability and use of POCTs.[14] The analyses of the availability of POCTs were conducted separately from the analyses of the use of POCTs.

For the analyses of the determinants of the availability of POCTs, the effect of characteristics of the workplace (i.e., the meso level) and country of work (i.e., the macro level) were assessed as the first and second levels of analysis, respectively. Clinician characteristics (such as years of practice, medical speciality, i.e., the micro level) were not assessed as the relative role of each respondent in the decision-making process leading to the availability of diagnostic tests in their workplace could not be measured.

For the analyses of the determinants of the use of POCTs, clinicians' characteristics combined with workplace characteristics were assessed as a single level of analysis (i.e., a combined meso-micro level of health systems was used as a first level of analysis) as most workplaces only had one clinician participating in the survey. An additional level of analysis which only assessed clinicians' characteristics would have required several clinicians to participate from each workplace. The country of work was again used a second level of analysis.

3.3.2. Qualitative analysis

The documents and interview transcripts were analysed thematically based on the seven domains of the NASSS framework.[15] The qualitative analyses were therefore mainly deductive in nature.

3.4. Synthesis

The quantitative and qualitative findings are summarised and synthesised in the discussion section of the thesis. The synthesis was achieved by comparing the results of the different studies in order to assess whether they converged and allowed for overall conclusions to be drawn. These conclusions were then used to provide recommendations for the implementation of POCTs in European settings and to suggests possible directions for future research.

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Chapter 4: (Research Paper 1) The availability and use of rapid diagnostic tests for the management of acute childhood infections in Europe: a cross-sectional survey of paediatricians

4.1. Introduction

This chapter addresses Objectives 1 and 2 of this thesis and aims to estimate the variability in the availability and use of current POCTs for the management of acute childhood infections across Europe, and to explore the determinants of this variability.

This research paper was published by PLOS One in December 2022. The manuscript and supplementary materials are presented in the following sections. A copy of the paper is provided as an Appendix to this thesis.

4.2. Citation

Dewez JE, Pembrey L, Nijman RG, Del Torso S, Grossman Z, Hadjipanayis A, et al. Availability and use of rapid diagnostic tests for the management of acute childhood infections in Europe: A cross-sectional survey of paediatricians. PLoS One. 2022;17(12):e0275336.

4.3. Cover sheet

The Research Paper Cover Sheet is enclosed in the following pages.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	210537	**Title**	Dr
First Name(s)	Juan Emmanuel		
Surname/Family Name	Dewez		
Thesis Title	The adoption of rapid diagnostic tests for the clinical management of acute childhood infections in European settings.		
Primary Supervisor	Professor Shunmay Yeung		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLoS ONE		
When was the work published?	20 December 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised the study with my primary supervisor. I developed the protocol and study materials, and obtained ethical approval, with inputs from my primary supervisor and co-authors. I built a partnership with several pan European and national paediatric associations to collect multi-country data. I conducted one of the pilot studies preceding the study. I managed data collection, and data cleaning. I conducted the analyses with inputs from my primary supervisor, Lucy Pembrey, James Burns, and Ruud Nijman. I drafted the manuscript which was reviewed and edited by all co-authors.I submitted the manuscript.

SECTION E

Student Signature	
Date	06 January 2023

Supervisor Signature	
Date	10th January 2023

4.4. Abstract

Background

Point-of-care-tests (POCTs) have been advocated to optimise care in patients with infections, but their actual use varies. This study aimed to estimate the variability in the adoption of current POCTs by paediatricians across Europe, and to explore the determinants of variability.

Methods and Findings

A cross-sectional survey was conducted of hospital and primary care paediatricians, recruited through professional networks. Questions focused on the availability and use of currently available POCTs. Data were analysed descriptively and using Median Odds Ratio (MOR) to measure variation between countries. Multilevel regression modelling using changes in the area under the receiver operating characteristic curve of models were used to assess the contribution of individual or workplace versus country level factors, to the observed variation.

The commonest POCTs were urine dipsticks (UD) which were available to >80% of primary care and hospital paediatricians in 68% (13/19) and 79% (23/29) countries, respectively. Availability of all POCTs varied between countries. In primary care, the country (MOR) varied from 1.61 (95%CI: 1.04-2.58) for lactate to 7.28 (95%CI: 3.04-24.35) for UD. In hospitals, the country MOR varied from 1.37 (95%CI:1.04-1.80) for lactate to 11.93 (95%CI:3.35-72.23) for UD. Most paediatricians in primary care (69%, 795/1154) and hospital (81%, 962/1188) would use a diagnostic test in the case scenario of an infant with undifferentiated fever. Multilevel regression modelling showed that the country of work was more important in predicting both the availability and use of POCTs than individual or workplace characteristics.

Conclusion

There is substantial variability in the adoption of POCTs for the management of acute infections in children across Europe. To inform future implementation of both existing and innovative tests, further research is needed to understand what drives the variation between

countries, the needs of frontline clinicians, and the role of diagnostic tests in the management of acute childhood infections.

4.5. Manuscript

4.5.1. Introduction

Fever is one of the commonest reasons for children to be presented to healthcare services.[1] Although most febrile children have self-limiting infections,[2,3] the consequences of severe infections can be catastrophic. The clinical features of infections in children are often non-specific making it difficult to identify which children require antibiotics and which children may deteriorate and therefore require referral or admission.[2] Diagnostic uncertainty and avoidance of risk contributes to unnecessary admissions, and over-prescription of antibiotics,[4] which may contribute to antimicrobial resistance.[5]

Point-of-care tests (POCTs) have the potential to improve patient care and antibiotic use depending on their accuracy, how quickly the results are available, how much they are trusted by the healthcare worker, and other factors. They have been widely advocated to reduce antibiotic resistance.[5]

Existing POCTs which can be performed by clinicians at the point of care are available in a number of formats including dipsticks, lateral flow tests, and table-top or handheld devices into which samples are introduced directly (e.g., blood gas analysers) or using a cartridge or test strip. Some tests can detect the presence of a pathogen, e.g., the Group A Streptococcus (GAS) rapid test; others measure the host reaction to infection, such as C-reactive protein (CRP) POCTs or White Blood Cell count; or do both, for example urine dipsticks (UD), which detect nitrites produced by bacteria, and the host's leucocyte-esterase.

Studies of the clinical effectiveness of using POCTs in the management acute childhood infections have mainly focused on their impact in reducing the use of antibiotics. A recent systematic review concluded that the use of GAS POCTs in primary care can reduce antibiotic prescription.[6] Other systematic reviews have found that the use of Influenza POCTs reduced the use of chest radiographs in children with respiratory infections in ambulatory care[7] and in emergency departments,[8] and that CRP POCTs may allow reducing the use of antibiotics

in children presenting with acute infections in primary care.[9,10] Another review found that urine dipsticks were effective in identifying children with urinary infections,[11] but it is unclear if their use leads to improved clinical outcomes. Evidence about the clinical effectiveness of using other POCTs in children with acute infections is lacking. In terms of cost-effectiveness, one study[12] showed that using urine dipsticks in primary care was not cost-effective in the United Kingdom, and, to the best of our knowledge, there are no cost-effectiveness studies assessing the use of other POCTs in children with acute infections in European settings.
There is evidence of wide variation in how children with acute infections are managed in selected emergency departments across Europe,[13,14] but limited data from a broader range of settings or focusing specifically on the availability and use of POCTs in this population. The use of POCTs in the management of adults in primary care varies,[15-21] but few studies aimed at understanding the reason behind this variation.

The landscape for rapid diagnostic tests is changing rapidly. In order to inform implementation of future and existing tests, this study aimed to estimate the variability in the availability and use of existing POCTs for the management of acute childhood infections across Europe by paediatricians working in primary care and in hospitals, and to explore the determinants of variability.

4.5.2. Materials and Methods

4.5.2.1. Study design and setting

An online cross-sectional survey of paediatricians from across Europe was conducted between September and November 2019.

4.5.2.2. Participants

The inclusion criteria were: clinically active paediatricians working in primary care or in a hospital in one of 29 countries in Europe in which the research team had collaborators (S1 Supplementary Materials).

Paediatricians were approached through research networks including the Personalised Risk assessment in febrile illness to optimise Real-life Management across Europe (PERFORM)

consortium, European Academy of Paediatrics Research in Ambulatory Settings network (EAPRASnet), European Society of Paediatric Infectious Diseases, Research in European Paediatric Emergency Medicine, and national associations of paediatrics.

Within each network, an email invitation with a web-link was sent to all members. Clicking on the link directed participants to a participant information sheet and consent form. After providing electronic consent, participants were directed to the start of the questionnaire. Three reminders were sent two weeks apart. Participation was monitored weekly, and in countries with low participation, national coordinators further disseminated the survey through professional networks. No incentives were offered.

4.5.2.3. POCTs and Outcome measures

For this study we focused on the availability and use of POCTs that can help frontline paediatricians to make clinical decisions within the timeframe of the consultation, i.e., usually performed (including sampling and processing of the sample) by the doctor or nurse close to the patient and with results available within around 15 minutes. The nine POCTs were selected by consensus of experts from 11 European countries based on their knowledge of current paediatric practice in their countries and the results of a first pilot study (see below). We did not restrict the inclusion of POCTs to those for which there is evidence of clinical and cost-effectiveness because we are interested in the current "real world" availability and use of POCTs.

The following nine POCTs were included:

- POCTs that detect the presence of a pathogen (antigen-based tests only):
    - Group A Streptococcus (GAS) rapid POCTs
    - Respiratory syncytial virus (RSV) antigen-based POCTs
    - Influenza antigen-based POCTs

- POCTs that measure the host reaction to infection:
    - Full blood count or white blood cell count POCTs
    - C-reactive protein (CRP) POCTs
    - Procalcitonin POCTs
    - Blood gas POCTs to measure acid base status +/- glucose +/- lactate

    - POCTs measuring lactate alone

- POCTs that detect the presence of pathogens and host reaction:
    - Urine dipsticks (for nitrites and leucocyte esterase)

More recent (PCR) based POCTs were not included because to our knowledge they were not being routinely performed by frontline clinicians in any setting; most have a turnaround of > 30 minutes and are performed in laboratories by technicians at fixed times of the day. Thus, they were felt to be outside the scope of the study.

The main outcomes of interest were the availability and use of existing POCTs used in the management of acute childhood infections in European settings. "Availability" was defined as the proportion of paediatricians reporting that the POCT was available in their workplace, and "use" was defined as the proportion of respondents who reported that they would use a POCT, if available, in a clinical scenario of an infant with undifferentiated fever (described below).

4.5.2.1. Questionnaires

The questionnaires were developed to estimate the outcomes and their association with different factors. To investigate the use of POCTs we used a clinical vignette, with the aim of replicating a common scenario in which there is diagnostic uncertainty. We therefore based the vignette on a 4-month-old infant not severely unwell, but febrile without a focus (S2 Supplementary Materials). Two similar questionnaires were developed in English, one for primary care and another for hospital paediatricians. These drafts were shared with paediatricians from 11 countries and adapted according to their feedback. The questionnaires were then piloted with 58 paediatricians at the 2017 European Academy of Paediatrics conference. Further revisions were made to improve the clarity and relevance of questions. The questionnaires were then translated into French, German, Greek, Hungarian, Italian, Latvian, Polish, Spanish, Slovenian, and Ukrainian, and then back translated into English by another blinded translator. The on-line English and Slovenian versions were piloted in Norway and Slovenia in June-July 2019 with 115 paediatricians. After correcting a few typographical errors and formatting, the final electronic formats were uploaded on the websites of the participating networks.

4.5.2.1. Sample size

A sample size of 1064 primary care paediatricians and 1787 hospital paediatricians was computed allowing for the estimation of the main outcomes with 90% confidence, a margin of error below 10%, and an expected proportion of the outcomes of 50% in each country. We also assessed and confirmed that these sample sizes would be sufficient to identify determinants of the main outcomes in multivariable logistic regression analyses (S1 Supplementary Materials).

4.5.2.1. Analysis

Descriptive statistics were used to derive individual and workplace (primary care practice or hospital) characteristics and estimates of the availability and use of POCTs per country.

Multilevel logistic regressions were performed to assess the associations of variables at different levels of determinants (namely at the level of the workplace and at the level of the country) and the availability of POCTs. Assessing the separate effects of these two levels is important because workplace characteristics vary across workplaces, while country characteristics (e.g., laws, health regulations) are assumed to be the same across all workplaces within a country (S3 Supplementary Materials for more explanations). For each POCT, we used a stepwise approach including three models based on the approach developed by Merlo and colleagues :[22] Model 1 was a simple logistic regression that included only workplace characteristics. This model was a base that was used as a comparator of Model 2. Model 2 was a multilevel logistic analysis which extended Model 1 by adding a second level, the country where the primary care practice or hospital was based. This multilevel analysis allows understanding the relative contributions of workplace characteristics and of country as a whole to the availability of POCTs. We compared the area under the receiver operating characteristic curve (AUC) of each model. Unlike clinical studies in which the change in AUC is often used to describe the increase in the accuracy of a diagnostic test, in this analysis the change in AUC between Models 1 and 2 is a measure of how the country as a whole contributes to predicting the availability of POCTs. If there is no change in AUC, the country as a whole does not contribute more than workplace characteristics; if there is an increase in AUC, this means that the country predicts better the availability of POCTs, and thus is a more important determinant. We also derived median

odds ratios (MOR) [22] to assess the magnitude of the variation of availability between countries. The MOR is the median value of the distribution of ORs obtained when randomly picking two workplaces with the same characteristics from two countries and comparing the one with the higher availability of POCTs to the one with the lower availability. The MOR reflects the change of odds of availability of a POCT if a workplace would be in another country. If the MOR=1, there is no change in odds. If the MOR>1, there is a variation across countries, and the larger the MOR the larger the variation is. Model 3 is an extension of Model 2 in which two country-specific characteristics (health expenditure per capita and financing scheme, see below) were added. While Model 1 and 2 assessed how much workplace characteristics and country as a whole explain the availability of POCTs, Model 3 sought to examine the extent to which the effect of country as a whole could be explained by the two measured country-specific characteristics. With regards the two country characteristics, we used 80% interval odds ratio (IOR80).[22] IOR80 were used because in multilevel analyses the ORs of the higher level variables (here the two country characteristics) only allow comparison of workplaces within a country but not across countries. The IOR80 overcomes this limitation. When the IOR80 includes one, the variable effect is considered as minor (S3 Supplementary Materials for more information). Model 3 was also used to assess the effect of workplace characteristics adjusting for county as a whole and for the two measured country characteristics, as these combined adjustments were not done in Models 1 and 2.

Directed acyclic graphs (DAGs) were developed to identify the variables that could be safely included in regression models to minimize confounding between the independent and dependent variables[23] (S4 Supplementary Materials). The workplace variables in primary care were: sector of activity (private/public), practice size (solo/ group practice), turnaround time for routine tests such as C-reactive protein or full blood count from the external laboratory (continuous), distance to this laboratory (continuous), and who takes bloods (doctor/another person). In hospitals the variables were: sector of activity (private/public), level of care (secondary/tertiary hospital), hospital specialty (general hospital/paediatric or women's and children's hospital), turnaround time from the hospital laboratory for routine tests such as C-reactive protein or full blood count (continuous), and who takes blood (doctor/another person). The country-specific variables were: health expenditure per capita (continuous), and main financing scheme (government/mandatory health insurance/voluntary insurance or out-of-pocket).

A similar stepwise approach was used to identify determinants of POCT use in the clinical scenario, but only the two first steps were used as the two country-specific variables were not considered to potentially be associated with the clinicians' decision to use POCTs. Model 4 included both workplace and clinicians' characteristics, and Model 5 was again an extension of Model 4 in which the country as a whole was included as a second level (S3 Supplementary Materials).

All participant questionnaires were included in the descriptive analyses. For the regression analyses, only questionnaires that provided data on the outcomes and potential explanatory variables were analysed (data flow chart in S5 Supplementary Materials).

Continuous variables were not categorised to avoid arbitrary cut-offs. Quadratic transformations were used when the relationship between continuous variables and the outcome was not linear, and when the quadratic variable improved the fit of the models. All continuous variables were centred at the mean value of the observations. The models were estimated using Markov chain Monte Carlo methods (MCMC) to obtain robust parameter estimates with 95% Credible Intervals. The deviance information criterion (DIC) was used to assess and compare the goodness of fit of the models. A difference of more than ten in DIC is considered to show significant differences between models.[24] Analyses were performed with Stata 16® and MLwin 3.05®.

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee (Ref: 15977).

4.5.3. Results

4.5.3.1. Participant characteristics

The study included 1154 primary care paediatricians from 19 countries, and 1188 hospital paediatricians from 504 unique hospitals from 29 countries (Fig 23 and data workflow in S5 Supplementary Materials). The response rate per network cannot be estimated because paediatricians might have been members of several networks. Almost half (46.4%, 535/ 1154) of the primary care paediatricians had practiced for 30 or more years, and only 7.6%

(88/1154) had practised for less than ten years. This compares with almost a quarter (22.4%, 266/1188) of the hospital paediatricians being trainees and 26.7% (317/1188) reporting less than ten years' experience. Of the hospital paediatricians, a quarter were general paediatricians (24.8%, 295/1188), and 14.6% (173/1188) were infectious disease specialists. Around one third of primary care paediatricians worked in solo practices (34.7%, 400/1154) and in the private sector (37.1%, 428/1154). Most of the hospital paediatricians (91.9%, 463/1154) worked in public hospitals (Table 3).

4.5.3.2. Availability of POCTs

There was large variation in the reported availability of different POCTs across countries with the variation being greater for some POCTs than others (Fig 24). In primary care, urine dipsticks and GAS POCTs were the most available test and were available to over 80% of paediatricians in 68% (13/19)

Figure 23. Origin of survey participants

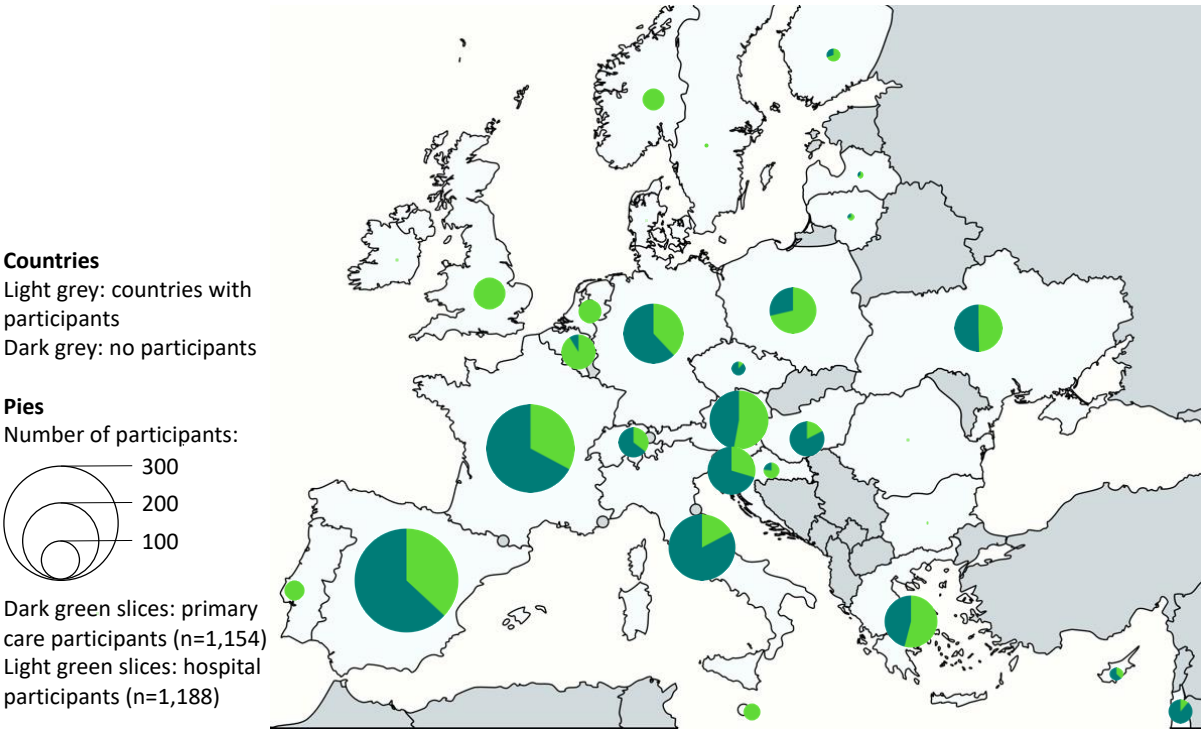


Table 3. Characteristics of survey participants and workplaces

Characteristics of participants					
	Primary care paediatricians n=1154 n (%)		**Hospital paediatricians n=1188 n (%)**		
Expertise	Paediatric trainee	22 (1.9)	Paediatric trainee	266 (22.4)	
	General paediatrician	1132 (98.1)	General paediatrician	295 (24.8)	
			Emergency medicine paediatrician	71 (6.0)	
			Infectious diseases paediatrician	173 (14.6)	
			Other paediatric subspecialty	383 (32.2)	
Years of clinical practice	<10	88 (7.6)	<10	317 (26.7)	
	10-<20	227(19.7)	10-<20	380 (32.0)	
	20-<30	304 (26.3)	20-<30	264 (22.2)	
	30-<40	418 (36.2)	30-<40	176 (14.8)	
	≥40	117 (10.1)	≥40	51 (4.3)	
Typical consultation time in busy periods of the year (minutes)	Median: 10 (IQR: 8 - 15)		Median: 15 (IQR: 15 - 20)		
Characteristics of workplaces					
	Primary care practices n=1154 n (%)		**Hospitals n= 504 n (%)**		
Sector of activity	Private sector	428 (37.1)	**Sector of activity**	Private sector	41 (8.1)
	Public sector	726 (62.9)		Public sector	463 (91.9)
Group or solo practice	Solo	400 (34.7)	**Hospital level of care**	Secondary care	244 (48.4)
	Group	754 (65.3)		Secondary and tertiary care	260 (51.6)

Distance to closest external laboratory (km)	Median: 1 (IQR: <1-5)		**Hospital specialty**	General hospital	334 (66.3)
				Paediatric or women's-and-children's hospital	170 (33.7)
Who takes bloods	Doctors	176 (15.3)	**Who takes bloods**	Doctors	128 (25.4)
	Other healthcare worker	682 (59.1)		Other healthcare worker	376 (74.6)
	Bloods not taken	296 (25.7)			
Shortest turnaround time for blood tests results from external lab (days)	Median: 1 (IQR: <1-5)		**Shortest turnaround time for blood tests results from hospital lab (minutes)**	Median: 60 (IQR:45-90)	

and 63% (12/19) of countries, respectively. Availability of other tests varied more, especially for CRP which was available to 40-79% of paediatricians in 42% (8/19) of countries, but to over 80% in 26% (5/19) of countries, and to under 20% of paediatricians in 10% (2/19) of countries. In hospitals, urine dipsticks were again the most available POCTs: in more than 80% of hospitals in 79% (23/29) of countries. Point-of-care blood gas analysis was also widely available with over 80% of paediatricians reporting it available in 65% (19/29) of countries. For other POCTs, availability varied greatly across different countries (S6 Supplementary Materials for estimates per country).

Importance of country of work on the availability of POCTs

The country of work was more important in predicting the availability of all POCTs in primary care and hospitals (except for lactate POCT) than workplace characteristics, as shown by the comparison of the AUC of Models 1 and 2 (AUC increase: 0.06-0.34) (Fig 25). The country median odds ratios (MOR) were greater than one for all POCTs (Fig 26A and 26B). For primary care it varied from 1.61 (95%CI: 1.04-2.58) for lactate to 7.28 (95%CI: 3.04-24.35) for urine dipsticks. This indicates that the median change in odds of availability would increase by a factor of 1.61 for lactate POCT and a factor of 7.28 for urine dipsticks when moving from a country with lower odds to a country with higher odds chosen at random and shows that

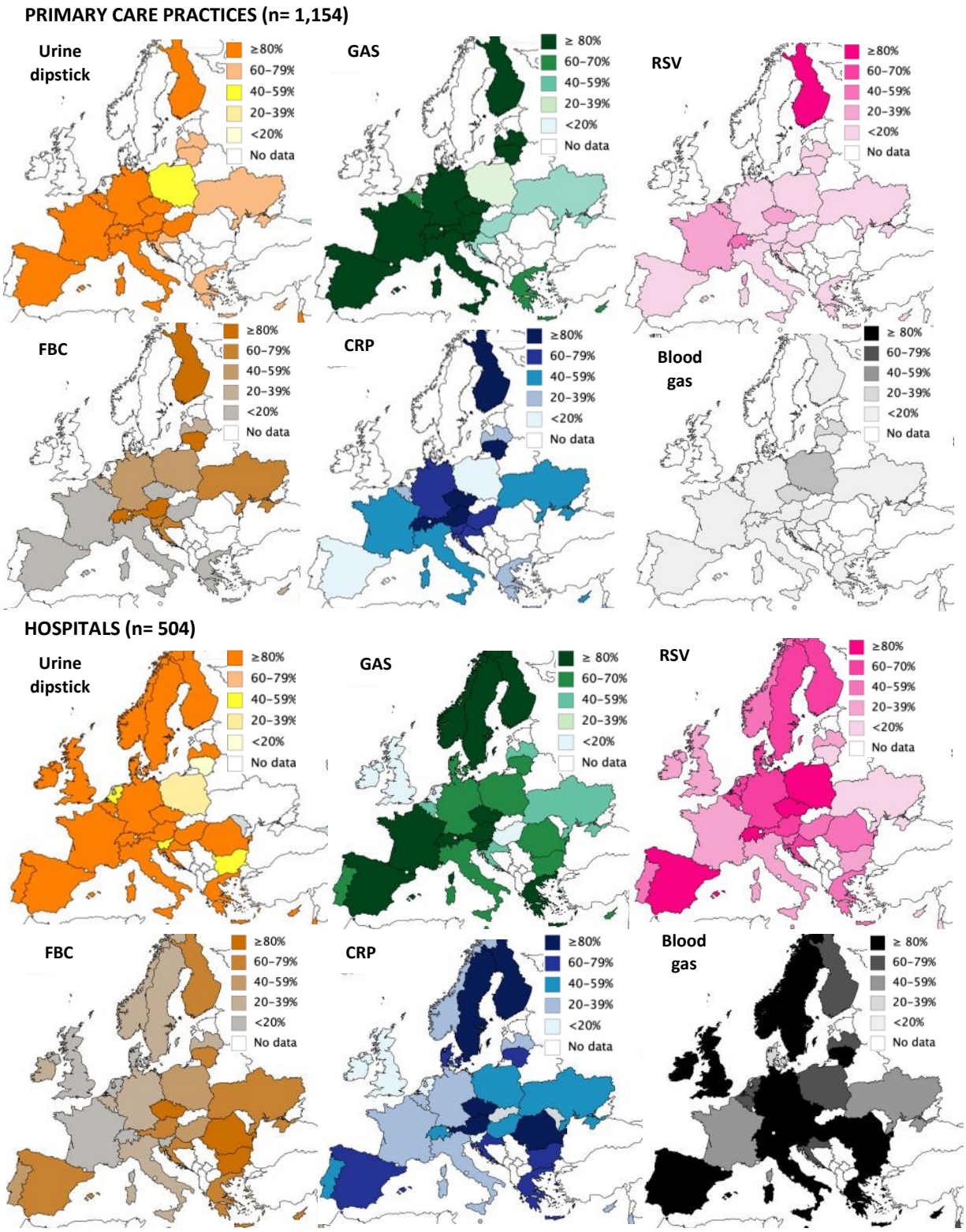
there is substantial between-country variation. For hospitals, the MOR varied from 1.37 (95%CI:1.04-1.80) for lactate to 11.93 (3.35-72.23) for urine dipsticks.

Effect of specific country and workplace characteristics on the availability of POCTs

In Model 3 the two measured specific country characteristics (health expenditure per capita and main financing scheme) showed no significant effects either in primary care or in hospitals (Table 4).

In terms of specific workplace characteristics, few variables showed a significant effect. In primary care, compared to public facilities, private practices had higher odds of availability of several POCTs including GAS (OR: 2.29, 95%CI: 1.07-4.39), RSV (OR: 2.36, 95%CI: 1.30-3.98), influenza (OR: 2.76, 95%CI: 1.71-4.22), and procalcitonin (OR: 2.32, 95%CI: 1.04-4.49) POCTs. Solo practices had lower odds of availability of GAS (OR: 0.50, 95%CI: 0.24-0.91), and CRP (OR: 0.61, 95%CI: 0.36-0.95) POCTs compared to group practices. A longer distance to the external laboratory was associated with lower odds of availability of FBC (OR per each km increase: 0.97, 95%CI: 0.95-0.98), procalcitonin (OR: 0.96, 95%CI: 0.91-0.99), blood gas (OR: 0.93, 95%CI: 0.88-0.97), and lactate (OR: 0.93, 95%CI: 0.87-0.98) POCTs. In hospitals, private hospitals had higher odds of availability of GAS (OR: 3.38, 95%CI: 1.21-8.00), FBC (OR: 2.57, 95%CI: 1.07-5.40), CRP (OR: 3.05, 95%CI: 1.29-6.31), and procalcitonin (OR: 2.83, 95%CI: 1.15-5.95) POCTs.

Figure 24. Percentage of paediatricians reporting availability of POCTs in each country



GAS: Group A Strep.; CRP: C-Reactive protein; FBC: Full blood count; RSV: Respiratory Syncytial Virus

4.5.3.3. Use of POCTS in the clinical scenario

69% (795/1154) of primary care paediatricians and 81% (962/1188) of hospital paediatricians reported they would use at least one diagnostic in the clinical scenario. UD, CRP, and influenza were the most commonly cited POCTs by primary care paediatricians (90%, 65%, and 51% of them, respectively), and hospital paediatricians (61%, 48%, and 50%, respectively) (S7 Supplementary Materials for estimates per country).

Importance of country as a whole on the reported use of POCTs in the clinical scenario

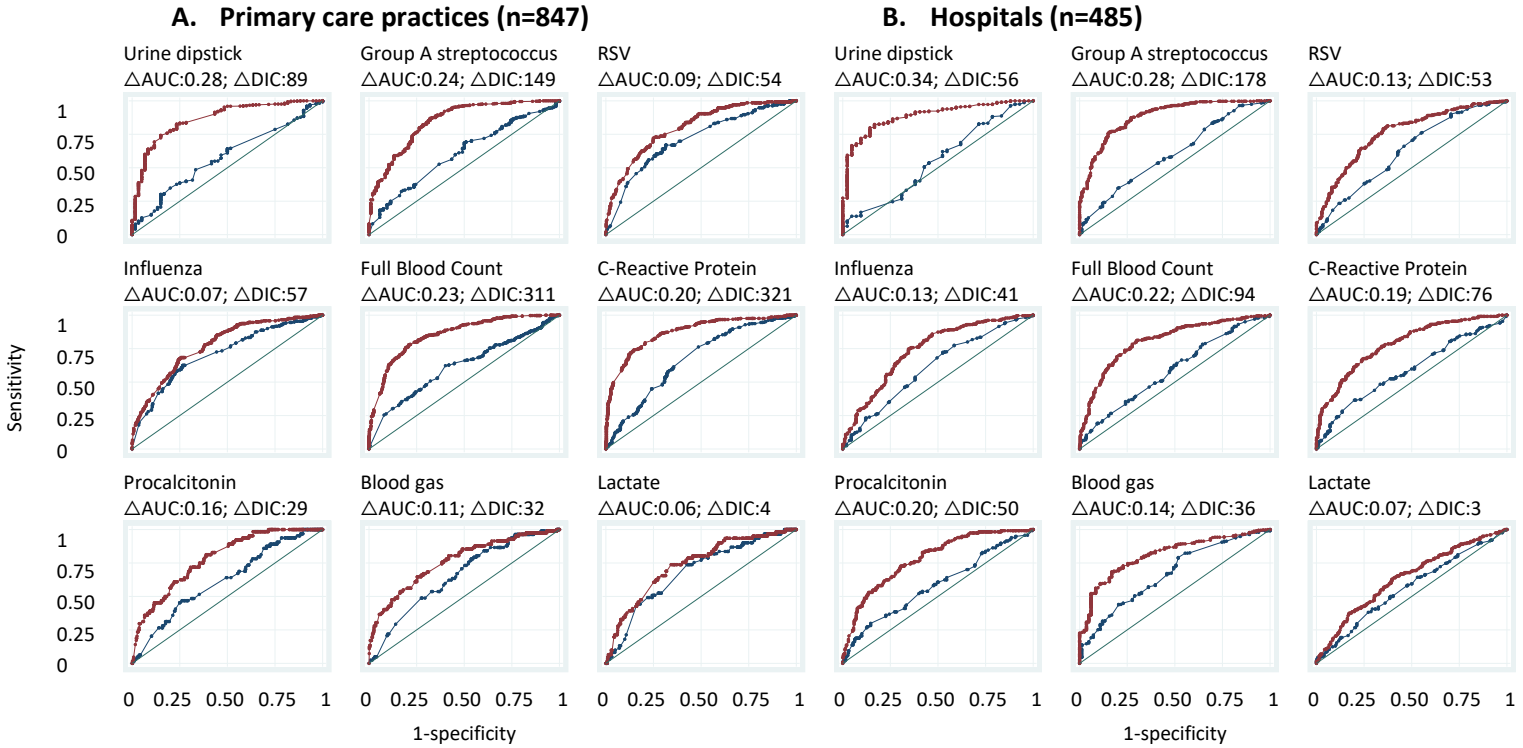
The comparison of Models 4 and 5 showed that adding the country improved the prediction of the use of all POCTs in the clinical scenario (AUC increase: 0.04-0.17), but this was not significant for lactate by primary care paediatricians, and for RSV, FBC, and CRP by hospital paediatricians (Fig 27). This shows again that the country as a whole is overall more important to predict the use of most POCTs than workplace and clinician characteristics, although the increases in AUC between Models 4 and 5 were smaller overall compared to the increases in AUC between models 1 and 2.

The country MOR was greater than one for all POCTs (Fig 28B and 28C). It varied from 2.00 (95%CI:1.03-5.13) for lactate to 4.49 (95%CI:2.01-12.26) for urine dipsticks use in primary care, and from 1.39 (95%CI:1.01-1.81) for CRP to 2.90 (95%CI:1.84-4.95) for blood gas use in hospitals.

Effect of specific workplace and clinician characteristics on the use of POCTs in the clinical scenario

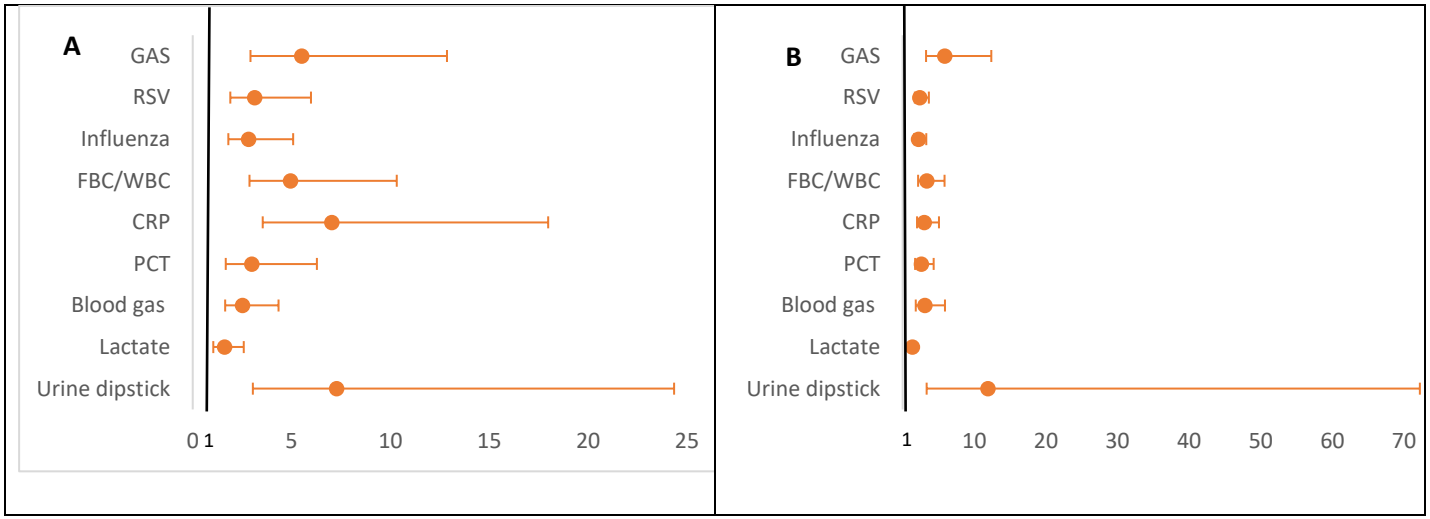
Few specific workplace or clinician characteristics showed a significant effect on the use of POCTs. In primary care, a longer turnaround time for diagnostics results by the external laboratory was associated with higher odds of using CRP POCT (OR: 6.20; 95%CI:1.55-18.01) and lactate POCTs (OR: 2.07; 95%CI:1.13-3.43) (Table 5A). In hospitals, clinicians working in paediatric or women and children hospitals had higher odds of using FBC (OR: 3.38, 95%CI: 1.21-8.00), and procalcitonin POCTs (OR: 3.38, 95%CI: 1.21-8.00) compared to those working in general hospitals. Working in a hospital where doctors take bloods was associated with higher odds of using bloods gas (OR: 2.44, 95%CI: 1.13-4.56), and lactate POCTs (OR: 2.47, 95%CI: 1.05-4.76) (Table 5B). No clinicians' characteristic was significant in either primary care or hospitals.

Figure 25. Area under the receiver operating curves (AUC) for the availability of POCTs in primary care practices and hospitals (Models 1 and 2)



Blue dots: model which adjusts for primary care practice or hospital characteristics (Model 1)
Red dots: Model 1 + adjustment for country of work (Model 2)
The diagonal line represents an AUC of 0.50, i.e., a model with no predictive power
△AUC: change in AUC when adding country of work (i.e., change in AUC when moving from Model 1 to Model 2)
△DIC: difference in Deviance Information Criterion. A △DIC>10 is considered a significant difference between models

Figure 26. Variation in the availability of POCTs between the included countries expressed as median odds ratio (MORs)



GAS: Group A streptococcus; RSV: Respiratory syncytial virus; FBC/WBC: Full blood count/White blood count; CRP: C-reactive protein; PCT: Procalcitonin
A: Country MORs for the availability of POCTs in primary care
B: Country MORs for the availability of POCTs in hospitals
MOR>1 indicate variation in the availability of POCTs across countries

Table 4. Effect of specific workplace and country level variables on the availability of POCTs in primary care practices and hospitals (Model 3)

A. Primary care practices (observations: 847)										
Primary care practice variables	**Statistic**	**Pathogen-based POCTs**			**Host-based POCTs**					**Pathogen and host-based tests**
		GAS	**RSV**	**Influenza**	**Full or white blood count**	**C-reactive protein**	**PCT**	**Blood gas**	**Lactate**	**Urine dipstick**
Private vs public primary care practice	OR (95% CrI)	2.29 (1.07-4.39)	2.36 (1.30-3.98)	2.76 (1.71-4.22)	0.80 (0.47-1.26)	1.64 (0.93-2.70)	2.32 (1.04-4.49)	0.99 (0.19-1.80)	1.75 (0.87-3.14)	1.91 (0.75-4.03)
Solo practice vs group practice	OR (95% CrI)	0.50 (0.24-0.91)	1.13 (0.66-1.80)	1.00 (0.64-1.49)	0.71 (0.42-1.11)	0.61 (0.36-0.95)	0.66 (0.25-1.37)	0.53 (0.24-1.00)	0.52 (0.21-1.04)	0.90 (0.37-1.86)
Distance to external laboratory (km)	OR (95% CrI)	1.00 (0.97-1.01)	0.95 (0.91-0.99)	0.97 (0.94-1.00)	0.97 (0.95-0.98)	0.99 (0.97-1.00)	0.96 (0.91-099)	0.93 (0.88-0.97)	0.93 (0.87-0.98)	0.97 (0.95-1.00)
Square distance to external laboratory*	OR (95% CrI)	NA	1.00 (1.00-1.00)	1.00 (1.00-1.00)	NA	NA	NA	NA	NA	NA
External laboratory turnaround time for routine tests**	OR (95% CrI)	0.76 (0.50-1.11)	1.47 (0.95-2.14)	1.11 (0.78-1.53)	1.01 (0.72-1.37)	1.20 (0.82-1.70)	1.32 (0.79-2.03)	0.88 (0.50-1.39)	1.81 (1.12-2.75)	1.47 (0.69-2.94)

Doctors take blood vs other health workers	OR (95% CrI)	NA	NA	NA	0.53 (0.30-0.85)	1.03 (0.57-1.73)	1.20 (0.43-2.60)	1.53 (0.70-2.89)	1.24 (0.49-2.50)	NA
Country level variables										
Health expenditure per capita	OR (95% CrI)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.99-1.00)
	IOR80	0.06-16.89	0.12-8.17	0.11-9.32	0.03-30.86	0.02-48.18	0.12-8.50	0.16-6.38	0.45-2.22	0.04-24.82
Government funding vs compulsory health insurance scheme	OR (95% CrI)	4.30 (0.33-18.07)	2.23 (0.35-7.94)	3.31 (0.22-18.76)	1.37 (0.95-6.36)	0.58 (0.02-2.94)	4.14 (0.66-16.42)	1.21 (0.26-3.97)	1.08 (0.41-2.65)	21.49 (0.67-129.46)
	IOR80	0.15-42.28	0.20-13.09	0.26-22.24	0.03-23.82	0.01-13.27	0.33-23.78	0.15-5.94	0.43-2.11	0.32-196.12
VHI-OOP vs compulsory health insurance scheme	OR (95% CrI))	4.15 (0.68-6.53)	7.50 (0.40-34.04)	4.04 (0.22-18.76)	4.07 (0.04-21.16)	1.87 (0.00-6.29)	4,18 (0.16-20.35)	2.55 (0.18-11.36)	1.25 (0.16-4.30)	4.74 (0.03-23.49)
	IOR80	0.06-17.93	0.44-29.40	0.22-19.36	0.03-28.35	0.00-8.52	0.21-14.89	0.23-9.17	0.40-1.98	0.04-26.62
	Country variance (95% CrI)	2.43 (0.68-6.53)	1.34 (0.33-3.70)	1.52 (0.46-3.81)	3.58 (1.42-8.26)	4.57 (1.71-11.01)	1.39 (0.19-4.48)	1.04 (0.23-2.89)	0.19 (0.00-0.97)	3.14 (0.49-10.79)
B. Hospitals (observations: 485)										
Hospital variables	**Statistic**	**GAS**	**RSV**	**Influenza**	**Full or white blood count**	**C-reactive protein**	**PCT**	**Blood gas**	**Lactate**	**Urine dipstick**
Private vs public	OR (95% CrI)	3.38 (1.21-8.00)	1.76 (0.72-3.72)	1.91 (0.80-4.01)	2.57 (1.07-5.40)	3.05 (1.29-6.31)	2.83 (1.15-5.95)	2.88 (0.91-7.60)	1.82 (0.88-3.38)	4.41 (0.81-16.09)

primary hospital										
Secondary vs tertiary level hospital	OR (95% CrI)	1.56 (0.84-2.66)	0.83 (0.51-1.28)	1.21 (0.75-1.86)	0.86 (0.51-1.38)	0.86 (0.52-1.32)	1.11 (0.63-1.84)	0.70 (0.35-1.23)	0.67 (0.43-1.00)	0.74 (0.29-1.56)
Paediatric/mother and child hospital vs general hospital	OR (95% CrI)	1.10 (0.55-1.88)	1.37 (0.79-2.20)	1.70 (1.01-2.73)	1.36 (0.77-2.24)	1.16 (0.67-1.87)	1.05 (0.57-1.78)	1.06 (0.52-1.95)	0.94 (0.58-1.43)	1.09 (0.38-2.48)
Hospital lab turnaround time for routine tests**	OR (95% CrI)	0.98 (0.96-0.99)	1.00 (1.00-1.00)	1.00 (0.99-1.00)	0.99 (0.98-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.01)
Square Hospital lab turnaround time for tests*	OR (95% CrI)	1.00 (1.00-1.01)	NA	NA	1.00 (1.00-1.01)	NA	NA	NA	NA	NA
Doctors take blood vs other health workers	OR (95% CrI)	NA	NA	NA	1.28 (0.57-2.53)	0.95 (0.40-1.96)	0.90 (0.34-1.89)	1.18 (0.34-2.96)	1.15 (0.65-1.84)	NA
Country level variables										
Health expenditure per capita	OR (95% CrI))	1.03 (0.97-3.89)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.29 (0.02-4.39)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
	IOR80	0.03-39.01	0.21-4.75	0.2-4.63	0.14-7.30	0.11-9.50	0.16-6.07	0.13-7.83	0.58-1.73	0.01-80.75
Government funding vs compulsory	OR (95% CrI)	8.78 (0.10-56.66)	0.62 (0.23-1.36)	0.62 (0.23-1.32)	1.08 (0.29-2.72)	0.99 (0.26-2.57)	13.17 (0.68-254.08)	2.07 (0.50-5.71)	1.19 (0.69-1.89)	2.36 (0.11-65.63)

health insurance scheme	IOR80	0.02-26.42	0.12-2.67	0.12-2.63	0.13-6.78	0.09-7.96	0.12-4.45	0.22-13.42	0.67-1.99	0.54-3498.27
VHI-OOP vs compulsory health insurance scheme	OR (95% CrI)	0.46 (0.03-6.99)	0.76 (0.10-2.69)	1.32 (0.19-4.68)	5.60 (0.40-25.72)	2.64 (0.19-11.83)	0.46 (0.03-6.99)	32.33 (0.85-182.54)	0.76 (0.23-1.91)	33.91 (4.23-1057.84)
	IOR80	0.06-96.36	0.11-2.55	0.20-4.38	0.42-22.46	0.16-14.35	0.07-2.73	1.28-78.46	0.38-1.14	0.03-202.12
	Country variance (95%CrI)	4.10 (1.73-8.61)	0.74 (0.26-1.67)	0.71 (0.23-1.67)	1.20 (0.42-2.79)	1.54 (0.58-3.40)	0.99 (0.31-2.42)	1.29 (0.31-3.44)	0.09 (0.00-0.36)	5.86 (1.03-20.61)

GAS: Group A Streptococcus; RSV: Respiratory syncytial virus; PCT: Procalcitonin; OR: Odds ratio; 95% CrI: 95 % Credible Interval; IOR80: 80% Interval odds ratio; MOR: Median odds ratio; VHI-OOP: Voluntary health insurance-out of pocket; NA: Not applicable

**Quadratic transformations were used when the relationship between continuous variables and the outcome was not linear, and when the quadratic variable improved the fit of the final models*

*** such as C-reactive protein or full blood count*

4.5.4. Discussion

4.5.4.1. Summary of findings

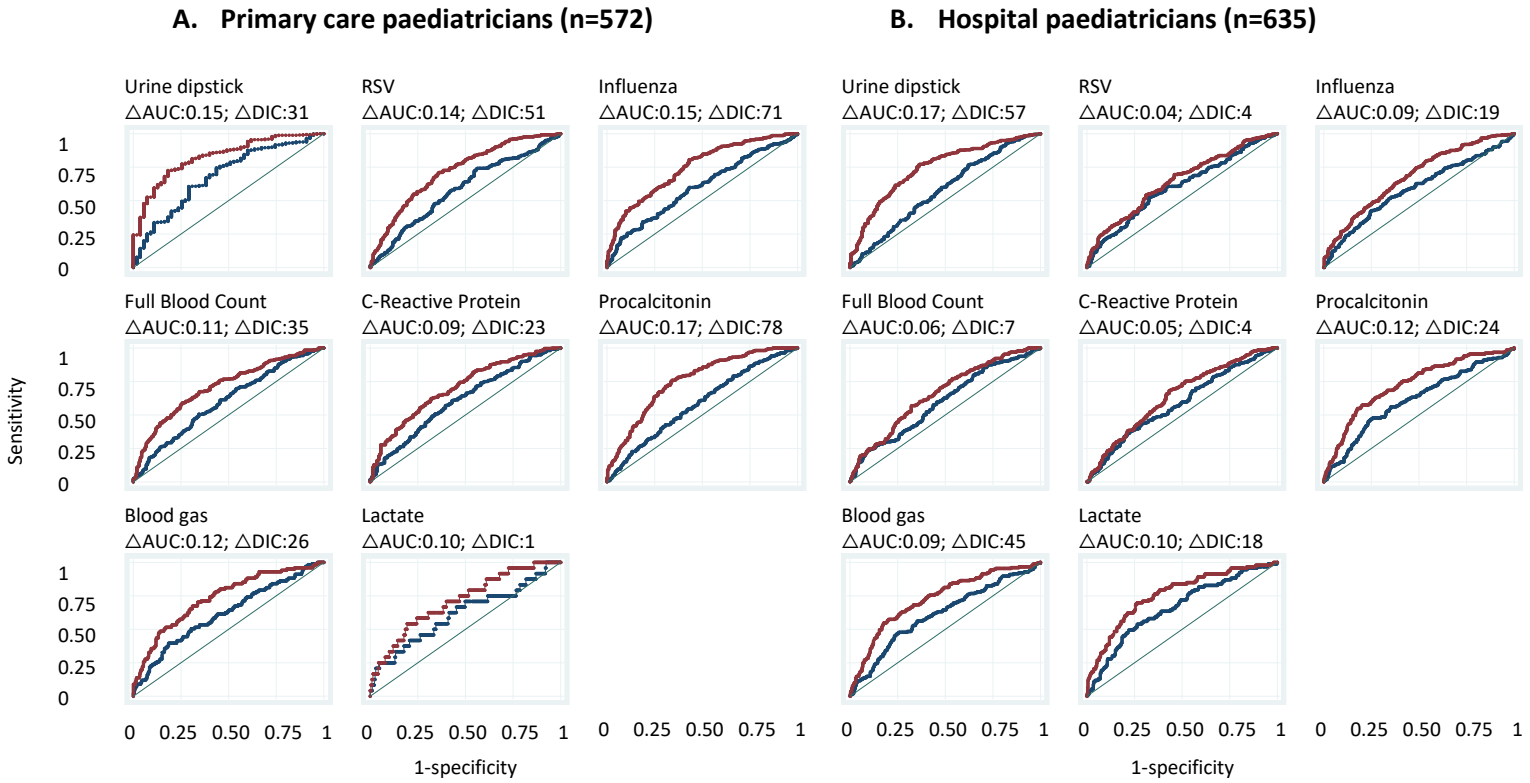
The availability and use of POCTs in the management of children with suspected infections varies substantially across Europe. By far the strongest determinant of whether or not POCTs are available to and used by paediatricians is the country in which they work. The reasons for this are likely to be complex and could not be simply explained by differences in how health care is financed within countries, nor overall healthcare expenditure per capita. The latter finding contrasts with other reports which have found that the availability of in vitro diagnostics overall, and of expensive diagnostics such as CT-scans or MRIs, are associated with health expenditure per capita.[25]

We found that operating as a private facility is associated with an increased odds of availability of some POCTs but was not associated with use in the clinical scenario. POCTs can be a source of income in these settings,[26,27] however in our study, the clinical scenario was a febrile infant which is unlikely to be the type of patient on which diagnostics would be overused to increase income.

The pattern of availability and use varied by type of POCT, but overall urine dipsticks and GAS were the most commonly available POCTs in primary care, while in hospitals it was urine dipsticks and blood gas POCTs. Previous studies have been limited in either the range of POCTs examined or the number of countries included. For urine dipsticks, previous studies have also reported their wide availability: a survey of paediatricians from eight countries found that 74% of paediatricians use UD [28], and a survey of GPs from Belgium, Holland, and the UK showed that they were available in 87%, 96%, and 90% of practices, respectively.[18] Reports on the availability of GAS POCT varied more. The above survey of GPs found that GAS POCTs were only available in 4%, 1%, and 15% of Belgian, Dutch, and British practices, respectively. By contrast, surveys of French GPs,[29] and of Spanish primary care paediatricians found that GAS POCT were available to 88% and 79% of participants, respectively,[30] which is in line with our findings for those countries.

In a clinical scenario of an infant with undifferentiated fever most paediatricians reported that they would use some kind of diagnostic tests with urine dipsticks, CRP, and influenza

Figure 27. Area under the receiver operating characteristic curves (AUC) for the use of POCTs in the clinical scenario by primary care and hospital paediatricians (Models 4 and 5)



Blue dots: models which adjusts for paediatricians and workplace characteristics (Model 4)

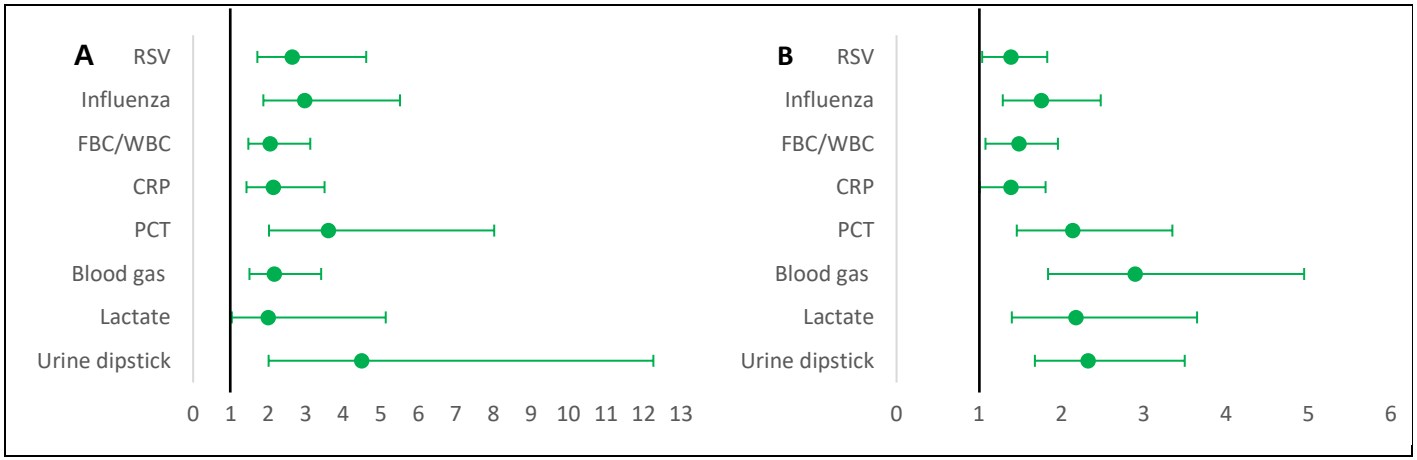
Red dots: Model 4 + adjustment for country of work (Model 5)

The diagonal line represents an AUC of 0.50, i.e., a model with no predictive power

△AUC: change in AUC when adding country of work (i.e., change in AUC when moving from Model 4 to Model 5)

△DIC: difference in Deviance Information Criterion. A △DIC>10 is considered a significant difference between models

Figure 28. Variation in the use of POCTs between the included countries expressed as median odds ratio (MORs)



GAS: Group A streptococcus; RSV: Respiratory syncytial virus; FBC/WBC: Full blood count/White blood count; CRP: C-reactive protein; PCT: Procalcitonin
A: Country MORs for the use of POCTs in primary care
B: Country MORs for the use of POCTs in hospitals
MOR>1 indicate variation in the use of POCTs across countries

Table 5. Effect of clinician, workplace variables, and country of work on the use of POCTs in the clinical scenario (Model 5)

A. Primary care (observations: 572)									
Clinician and primary care practice variables	**Statistic**	**Pathogen-based POCTs**		**Host-based POCTs**					**Pathogen and host-based tests**
		RSV	**Influenza**	**Full or white blood count**	**C-reactive protein**	**PCT**	**Blood gas**	**Lactate**	**Urine dipstick**
Years of clinical practice	OR (95% CrI)	1.00 (0.98-1.02)	0.99 (0.97-1.01)	1.13 (1.04-1.22)	1.01 (0.99-1.03)	1.08 (1.00-1.17)	0.90 (0.82-0.99)	1.01 (0.98-1.06)	1.05 (1.02-1.08)
Square years of clinical practice*	OR (95% CrI)	NA	NA	1.00 (1.00-1.00)	NA	1.00 (1.00-1.00)	1.00 (1.00-1.00)	NA	NA
Average consultation time	OR (95% CrI)	1.00 (0.97-1.03)	1.01 (0.97-1.04)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	1.00 (0.96-1.04)	1.00 (0.96-1.04)	0.97 (0.88-1.04)	0.98 (0.94-1.03)
Private practice vs public practice	OR (95% CrI)	0.90 (0.52-1.46)	0.86 (0.49-1.39)	1.36 (0.79-2.21)	1.78 (1.02-2.93)	1.22 (0.67-2.05)	0.71 (0.36-1.26)	1.30 (0.34-3.34)	2.72 (0.95-6.58)
Solo practice vs group practice	OR (95% CrI)	1.36 (0.83-2.13)	0.93 (0.56-1.44)	0.95 (0.58-1.49)	0.88 (0.51-1.41)	0.98 (0.57-1.57)	1.11 (0.58-1.91)	0.70 (0.16-1.85)	2.04 (0.74-4.79)
Distance to external laboratory	OR (95% CrI)	1.00 (0.99-1.02)	1.00 (0.98-1.02)	0.99 (0.97-1.00)	0.99 (0.97-1.01)	1.00 (0.98-1.02)	0.99 (0.97-1.01)	0.99 (0.95-1.03)	1.00 (0.97-1.03)
External lab turnaround time for routine tests**	OR (95% CrI)	1.23 (0.88-1.68)	1.34 (0.94-1.85)	1.30 (0.93-1.78)	6.20 (1.55-18.01)	0.85 (0.59-1.18)	1.46 (0.97-2.11)	2.07 (1.13-3.43)	0.92 (0.47-1.65)

Square external lab turnaround time*	OR (95% CrI)	NA	NA	NA	0.71 (0.51-0.93)	NA	NA	NA	NA
Doctors take blood vs other health workers	OR (95% CrI)	NA	NA	0.67 (0.38-1.10)	1.06 (0.58-1.78)	1.15 (0.64-1.92)	1.94 (0.99-3.42)	1.14 (0.23-3.22)	NA
Country									
	Country variance (95%CrI)	1.03 (0.32-2.57)	1.30 (0.42-3.20)	0.57 (0.16-1.42)	0.64 (0.13-1.72)	1.80 (0.54-4.76)	0.65 (0.18-1.65)	0.52 (0.00-2.94)	2.48 (0.54-6.90)
B. **Hospitals (observations: 635)**									
Clinician and hospital variables	**Statistic**	**RSV**	**Influenza**	**Full or white blood count**	**C-reactive protein**	**PCT**	**Blood gas**	**Lactate**	**Urine dipstick**
Years of clinical practice	OR (95% CrI)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.00 (0.98-1.03)	1.02 (1.00-1.04)	1.02 (0.99-1.04)	0.98 (0.95-1.00)	1.00 (097-1.03)	1.00 (0.98-1.02)
Trainee doctor vs general paediatrician	OR (95% CrI)	1.80 (0.99-3.08)	1.03 (0.56-1.74)	1.21 (0.65-2.11)	1.52 (0.85-2.56)	1.23 (0.57-2.34)	0.35 (0.17-0.66)	0.73 (0.29-1.54)	1.31 (0.67-2.30)
Specialist vs general paediatrician	OR (95% CrI)	1.56 (0.99-2.39)	1.29 (0.81-1.95)	0.62 (0.38-0.95)	0.93 (0.60-1.40)	1.45 (0.83-2.39)	0.92 (0.53-1.49)	0.96 (0.49-1.72)	1.25 (0.76-1.94)
Average consultation time	OR (95% CrI)	1.00 (0.98-1.02)	1.00 (0.98-1.01)	0.99 (0.97-1.01)	1.01 (1.00-1.03)	1.01 (0.99-1.03)	1.02 (1.00-1.05)	1.03 (1.00-1.05)	0.99 (0.97-1.01)
Private vs public primary hospital	OR (95% CrI)	1.52 (0.66-3.06)	1.34 (0.58-2.69)	1.57 (0.64-3.20)	1.23 (0.54-2.39)	2.09 (0.82-4.37)	0.82 (0.26-1.89)	1.47 (0.38-3.58)	1.17 (0.47-2.48)

Secondary vs tertiary level hospital	OR (95% CrI)	0.91 (0.60-1.32)	1.14 (0.75-1.66)	1.03 (0.65-1.55)	1.12 (0.74-1.61)	1.15 (0.69-1.81)	0.85 (0.51-1.32)	1.22 (0.66-2.07)	0.66 (0.41-1.01)
Paediatric/ women's and children's hospital vs general hospital	OR (95% CrI)	1.31 (0.87-1.92)	1.49 (0.97-2.19)	1.67 (1.05-2.56)	1.25 (0.82-1.81)	1.74 (1.04-2.77)	1.09 (0.65-1.74)	1.29 (0.68-2.22)	0.96 (0.58-1.49)
Hospital lab turnaround time for routine tests**	OR (95% CrI)	1.01 (1.00-1.02)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Square hospital lab turnaround time for tests*	OR (95% CrI)	1.00 (1.00-1.00)	NA	NA	NA	NA	NA	NA	NA
Doctors take blood vs other health workers	OR (95% CrI)	NA	NA	1.30 (0.75-2.04)	1.20 (0.73-1.81)	1.47 (0.73-2.71)	2.44 (1.13-4.56)	2.47 (1.05-4.76)	NA
Country									
	Country Variance (95%CrI)	0.12 (00-0.41)	0.35 (0.07-0.91)	0.17 (0.01-0.49)	0.12 (0.00-0.38)	0.64 (0.16-1.60)	1.25 (0.41-2.81)	0.67 (0.12-1.84)	0.79 (0.29-1.72)

RSV: Respiratory syncytial virus; PCT: Procalcitonin; OR: Odds ratio; 95%; CrI: 95 % Credible Interval; MOR: Median odds ratio; NA: Not applicable

**Quadratic transformations were used when the relationship between continuous variables and the outcome was not linear, and when the quadratic variable improved the fit of the final models*

*** such as C-reactive protein or full blood count*

being the most commonly cited POCTs in both settings. This is in line with a study of children attending EDs in eight countries which found that 78% of infants with undifferentiated fever were tested.[14]

4.5.4.2. Strength and limitations

Main strengths of this study are its size and breadth, that it addresses an important but under-researched question, and employed a robust approach to both the study design and analysis.

We included a large number of community- and hospital-based paediatricians from many countries across Europe and sought to be as complete in our sampling as possible. However, we did not manage to achieve our pre-defined sample size for the analysis about the use of POCTs and given the sampling approach there is a possibility of selection bias. Due to resource constraints, we limited the scope of this study to paediatricians and did not extend it to General Practitioners, who in some countries are the main providers of medical care for children in the community.

The survey was developed through a robust process including the expertise of paediatricians from 11 countries, two pilot studies, the translation of the questionnaires into ten languages, and the use of software with quality-assurance checks. In order to maximise participation and completion rates we kept the questionnaire as short as possible. We therefore limited the clinical scenario to just one case, limiting generalisability of the findings about how paediatricians would use POCTs. We also omitted important topics or questions, for example the influence of evidence (or the lack of) on participants decision in the clinical scenario, or the perceptions about quality assurance. We used turnaround time for routine tests such as C-reactive protein or full blood count as a proxy for the time needed to obtain results from the closest laboratory in general, but turnaround times can vary substantially across different tests. We used the Bayesian MCMC methods to compute robust parameter estimates and direct acyclic graphs (DAGs) in order to identify the variables that could be safely included in the regression models while minimising confounding. However, the risk of confounding cannot be eliminated as DAG cannot entirely accurately represent reality.

4.5.4.3. Implication for the implementation of POCTs and future research

As mentioned earlier we found substantial variability in the availability and use of current POCTs between European countries that we were not able to explain but is likely to be due to complex interplay of different factors in each country. This might include differences in patient care pathways, the capacity and readiness to innovate, the processes to identify new technologies, the availability of resources including funding, the existence of alternative diagnostic tools, as well as diversity in policies and regulations, including quality assurance standards for the use of diagnostic tests. Moreover, the implementation of innovations, including POCTs, can be disruptive for healthcare services because they may impact on the roles of healthcare workers (because they may need to change their practice), on the routine organisations of health services, on the allocation of funding (funding for the innovation could be at the expense of funding other interventions), and the work needed to normalise the innovation can be substantial (e.g. training all staff that are already very busy).[31] From a rational national health systems perspective, the choice of which medical interventions should be implemented, should ideally be based on an assessment of their clinical-effectiveness, cost-effectiveness, and the broader impacts on health services – part of the remit of Health Technology Assessment organisations. Most of the available evidence on current POCTs, however, focuses on diagnostic test accuracy[32] and as mentioned in the introduction, current evidence about the use of POCTs in children is available only for few POCTs. The lack of such evidence means that the decision to implement diagnostic tests is more likely to be influenced by other factors which are specific to each country and local HTA processes.[33] There are around 50 HTA agencies across Europe,[34] and they may use different processes and criteria when assessing new diagnostic test. Additional in-depth studies are needed to understand how specific country factors influence the availability of POCTs in specific countries.

Once POCTs are made available, whether or not clinicians use them could vary depending on factors including clinicians' perceptions of the added value of the tests in, for example, reducing diagnostic uncertainty,[35] or their user friendliness. The practices and perception of paediatricians about the use of current POCTs in children with acute infections need also to be explored and compared across Europe through qualitative methods.

The study focussed on the POCTs that were being performed routinely by frontline line clinicians in some study countries at the time of the survey. Since then, change in diagnostic

landscape has accelerated dramatically in part due to the impact of the COVID-19 pandemic. Use of POCTs has become much more widespread, as has the availability of multiplex tests that are able to identify the presence of multiple pathogens.[36] Innovative "-omics" based tests which focus on differentiating bacterial from viral infections,[37,38] and multiclass tests[39] are under development. How these can impact on reducing diagnostic uncertainty and improving patient management is not clear, and further studies aimed at exploring how existing and new tests should be optimally deployed would be extremely useful. One drawback of pathogen-based tests is that the presence of microorganisms does not necessarily mean they are the cause of disease. Tests that measure the host's response to specific pathogens[40] or combine the detection of microorganism with the measurement of host biomarkers may be most useful in this regard. In terms of the management of children with acute infections, we believe that the main diagnostic gaps that need to be addressed is the prediction of severity. This would be particularly useful in children with substantial diagnostic uncertainty, such as young infants with undifferentiated fever, children with low respiratory infections in the "grey zone" (i.e., not severely ill, but raising some concern), or vulnerable children (e.g., immunocompromised children) presenting an episode of acute fever. European paediatricians and other healthcare workers who see children in consultation may have additional needs in terms of diagnostic tools. Additional studies aiming at identifying these needs would be important to inform the development of new tests. Ideally, once new tests are developed, studies aiming to assess all the different steps in the evaluation of diagnostic tests suggested by Horvath and colleagues[41] should be undertaken. This includes, as mentioned above, diagnostic test accuracy studies, clinical effectiveness studies, cost-effectiveness studies, and operational research studies estimating the diffusion of new tests across European countries and evaluating the implementation of the tests in specific national contexts. Finally, given that diagnostics tests are most often developed for and tested in adults[42] it is important that all of the aforementioned research is conducted with a specific focus on the use of the tests in children.

4.5.5. Conclusions

There is substantial variability in the adoption of POCTs for the management of acute infections in children across Europe. To inform future implementation of both existing and innovative tests, further research is needed to understand what drives the variation between

countries, the needs of frontline clinicians, and the role of diagnostic tests in the management of acute childhood infections.

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4.6. Supplementary materials

S1 Supplementary Materials: List of included countries and sample size per country

Table I. Sample sizes to estimate the main outcomes (current availability of CRP POCT, and use of CRP POCT in a clinical scenario) with 90% confidence, a margin of error below 10%, and an expected proportion of the outcomes of 50%

Country	Total population of primary care paediatricians *	Sample size of primary care paediatricians	Total population of hospital paediatricians*	Sample size of hospital paediatricians
Austria	585	61	774	62
Belgium	782	65	781	65
Bulgaria	NA	NA	1,475	65
Croatia	281	55	583	61
Cyprus	180	49	68	34
Czech Rep.	753	62	669	61
Denmark	NA	NA	469	59

Finland	73	35	623	61
France	1,453	65	6,622	67
Germany	5,991	67	7,924	67
Greece	2,128	65	2,130	65
Hungary	939	63	1,432	65
Ireland	NA	NA	451	59
Israel	501	60	1,699	65
Italy	6,000	67	11,354	67
Latvia	10	9	238	53
Lithuania	40	25	676	61
Malta	NA	NA	81	37
The Netherlands	NA	NA	1,751	65
Norway	NA	NA	875	63
Poland	5,040	67	9,905	67
Portugal	NA	NA	2,085	66
Romania	NA	NA	2,655	66
Slovenia	252	53	396	58
Spain	4,800	67	7,589	67
Sweden	NA	NA	1083	64
Switzerland	978	63	839	63
Ukraine	3,321	66	6,236	67
United Kingdom	NA	NA	10,464	67
TOTAL	34,107	1,064	81,927	1,787

*Source: Eurostat 2019 (available from https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_rs_phys&lang=en, accessed 03/12/19) and European Confederation of Primary Care Paediatricians 2018 (ECPCP, available from: https://www.ecpcp.eu, accessed 10/10/19), except for Spain and Poland, where figures were not available and provided by local partners.

NA: not applicable

In addition to the sample size estimates provided in the main manuscript, we also assessed whether these sample sizes would also allow identification of determinants of the main outcomes of interest with sufficient statistical power in multiple logistic regression analyses. Based on a rule of thumb of doubling the sample size to allow for multivariable analyses, we considered that if half of the sample sizes in Table I would allow detection of a difference in the main outcomes of interest between categories of the main hypothesised explanatory variables (health expenditure per capita for CRP POCT availability, and years of clinical experience for CRP POCT use), with >90% power, then the full samples sizes presented in Table I would also be sufficient for the regression analyses. With regards the determinants of CRP POCT availability, we grouped countries into two categories of health expenditure per capita (HEC): category 1 grouped countries spending ≤2,800 Euros per capita and category 2 countries spending >2,800 Euros, as 2,800 Euros is the median HEC of the countries included in the study[1,2] (Table II). We hypothesised that CRP POCT would be available to 50% of clinicians in the >2,800 Euros group based on the published availability of CRP POCT in the the Netherlands,[3] compared to 25% in the ≤2,800 Euros. The power to detect a difference between the two groups (with 283 primary care paediatricians in the ≤2,800 Euros category versus 241 in the >2,800 category, and 407 hospital paediatricians in the ≤2,800 Euros category versus 475 in the >2,800category, Table II) would be 100% in both primary care and hospital settings. With regards the determinants of CRP POCT use in the clinical scenario, we grouped participants into two categories: category 1 grouped participants with ≤ 10 years of experience, category 2 participants with >10 years of experience.[4] We considered that 20% of the sample will have ≤10 years of experience, based on European figures of years of experience of medical doctors.[5] We hypothesised that less experienced paediatricians would use CRP POCT in 45% of patients in the clinical scenario, while more experienced paediatricians will do so in 25% of patients, based on the rate of CRP use in febrile infants from 12 European hospitals members of the PERFORM consortium.[6] The power to detect a difference between the two groups (with 105 primary care paediatricians in the ≤10 years of experience category versus 419 in the >10 years of experience category, and 176 hospital paediatricians in the ≤10 years of experience category versus 706 in the >10 years of experience category, Table III) would be 97% in primary care and 100% in hospital settings. Thus, we were confident that the sample sizes in table I would ensure that the planned regression analyses have sufficient power.

Table II. Expected number of participants and health expenditure per capita categories

Country	Health expenditure per capita per year category (Euros)	Half of primary care paediatricians' sample size	Half of hospital paediatricians' sample size
Bulgaria	≤2,800	NA	32
Croatia		27	30
Cyprus		24	17
Czech Rep.		31	30
Greece		32	32
Hungary		31	32
Israel		30	32
Latvia		4	26
Lithuania		12	30
Malta		NA	18
Poland		33	33
Romania		NA	33
Slovenia		26	29
Ukraine		33	33
Sub total		**283**	**407**
Austria	>2,800	30	31
Belgium		32	32
Denmark		NA	29
Finland		17	30
France		32	33
Germany		33	33
Italy		33	33
Ireland		NA	29
The Netherlands		NA	32
Norway		NA	31
Portugal		NA	33
Spain		33	33
Switzerland		31	31
Sweden		NA	32
United Kingdom		NA	33

Subtotal		**241**	**475**
TOTAL		**524**	**882**

NA: not applicable

Table III. Expected number of participants and years of clinical experience

Years of clinical experience	Half of primary care paediatricians' sample size (all countries)	Half of hospital paediatricians' sample size (all countries)
Any experience	524	882
<10 years of practice (20% of any experience)[5]	105	176
>10 years of practice (80% of any experience)[5]	419	706

S2 Supplementary Materials: questionnaire (hospital questionnaire)

THE USE OF RAPID POINT-OF-CARE TESTS FOR MANAGING ACUTE CHILDHOOD INFECTIONS IN EUROPE

PARTICIPANT INFORMATION AND CONSENT FORM

The aim of the study is to estimate and compare the availability and use of rapid point-of-care tests for the management of acute childhood infections across Europe. **Rapid point-of-care tests are tests that are carried out in the consultation room (or in an adjacent room), with results available within the consultation timeframe.**

The study is conducted by the European Academy of Paediatrics Research in Ambulatory Settings Network (EAPRASnet) and researchers from the London School of Hygiene and Tropical Medicine (LSHTM). EAPRASnet is a practice-based research network whose mission is to improve the health of European children n and enhance the quality of primary care paediatrics. The LSHTM is a university specialised in global and public health research. The study is part of PERFORM, a large research collaboration which aims to develop new tests to for management of children with febrile illness.

We are recruiting physicians from across Europe who regularly treat children with acute infections.

The survey should take approximately 10 minutes to complete.

Your participation will help understand how physicians use rapid point-of-care tests in children with infections. We will ask questions on the availability of these tests; we will then ask you to comment on a clinical scenario; and we will finish with questions regarding future diagnostic tests.

There are no risks in taking part in the survey. The aim of the survey is not to assess the quality of your work.

All information collected in this study will be anonymised and kept confidential. Your responses will be combined with those of other respondents in reports and potential publications in peer-reviewed medical journals. Your response may be used for future research use as well. LSHTM will keep the information you provided for 10 years after the study has finished. You can withdraw from the study at any time without providing a reason.

Please tick the box below to confirm that you consent to the data being used in the way described here. If you have any questions regarding this survey, please contact: perform2020@lshtm.ac.uk or info@eaprasnet.org

□ YES, I have read and consent to the data being used in the way described above

SECTION A: GENERAL INFORMATION ON RESPONDENT AND SETTING

A00 Which professional societies/networks are you a member of? TICK ALL THAT APPLY

□ I am not a member of any professional societies/networks

□ The national society of paediatrics

□ A sub-national (e.g. regional) society of paediatrics

□ A national society of paediatric emergency medicine

□ A national society of paediatric infectious diseases

□ A national society of primary care paediatrics

□ A national society of junior paediatricians

□ A national society of general practice/family medicine

□ European Academy of Paediatrics-EAP

□ EAP Research in Ambulatory Settings Network-EAPRASnet

□ European Society of Paediatric Infectious Diseases-ESPID

□**Other(s), including other European societies, please specify:**

A01 What is your job? TICK ONE BOX

□ Paediatric trainee **GO TO QUESTION A03**

□ General paediatrician **GO TO QUESTION A03**

□ Paediatrician with subspecialty or special interest **GO TO QUESTION A02**

□ Emergency doctor for adults AND children **GO TO QUESTION A03**

A02 Please indicate your main subspecialty or special interest: TICK ONE BOX

□ Allergy

□ Cardiology

□ Endocrinology

□ Emergency medicine

□ Gastroenterology

□ Immunology / Infectious diseases

□ Intensive care

□ Neonatology

□ Nephrology

□ Neurology

□ Neurodevelopment

□ Oncology

□ Respiratory paediatrics

□ Rheumatology

□ **Other, please specify:**

A03 What year did you qualify from medical school (before starting the paediatric or emergency medicine training)?

About your main workplace

A04 Are most of your patients from an…? TICK ONE BOX

□ Urban area

□ Rural area

□ Mixed urban-rural area

A05 Is your work primarily in the private or public sector? TICK ONE BOX

□ Private

□ Public

A06 In which hospital department do you mainly work? TICK ONE BOX

□ Outpatient department

□ Paediatric Emergency Department

□ Emergency Department (for adults & children)

□ Paediatrics ward

□ **Other, please specify**:

A07 Which of the following best describes your hospital? TICK ONE BOX

□ Hospital providing secondary care only

□ Hospital providing secondary, and tertiary care

A08 Which of the following best describes your hospital? TICK ONE BOX

□ Paediatric or women and children hospital

□ General hospital

A09 Who usually takes blood for routine tests, like C-reactive protein or full blood count? TICK ONE BOX

□ Nurses

□ Doctors

□ Laboratory technicians

□ Phlebotomists or others

A10 What is the shortest turnaround time to get results of blood tests such as C-reactive protein or full blood count sent to the hospital lab?

A11 What is your hospital's name and city?

This question is not mandatory; it will help us knowing whether participants are from the same or different institutions. The name of the hospital will not be used in reports

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A12 On average, how long are your consultations during busier times of the year (in minutes)?

SECTION B: AVAILABILITY AND USE OF RAPID POINT-OF-CARE TESTS FOR THE CLINICAL MANAGEMENT OF INFECTIONS IN CHILDREN

This section assesses the general availability and use of rapid point-of-care tests (POCTs), regardless of who pays for it. Rapid point-of-care tests are tests performed in the consultation room, or in another room in your department, with results available during the consultation timeframe.

Which of the following diagnostic tests are usually available as POCTs in your workplace? If not available, please indicate if you would like the test for use in children TICK ONE BOX PER ROW

RAPID POINT-OF-CARE TESTS (POCT)	This POCT is **available and I do use** it in children	This POCT is **available, but rarely used** in children	This POCT is **NOT available; I would like it** available	This POCT is **NOT available; I don't think I need it**
B01 **C-Reactive protein**	□	□	□	□
B02 **Procalcitonin**	□	□	□	□
B03 **Full blood cell count or white blood cell count**	□	□	□	□
B04 **Blood gas (with or without lactate)**	□	□	□	□
B05 **Lactate alone**	□	□	□	□
B06 **Urine dipstick**	□	□	□	□
B06.2 **Microscopy in the clinical area***	□	□	□	□
*In some hospitals, microscopes are available on the ward and clinicians look at urines directly using the microscope. In that case the microscope is a rapid point-of-care test.				
B07 **Influenza virus rapid antigen**	□	□	□	□
B08 **Respiratory Syncytial Virus rapid antigen**	□	□	□	□

B09 **Group A streptococci rapid antigen (throat swab)**	□	□	□	□

B10 Are there other rapid point-of-care tests that are available to you in your workplace, for the clinical management of infections in children? TICK ONE BOX

□ No

□ Yes, specify:

SECTION C: CLINICAL SCENARIO

A 4-month old infant is brought to see you in the early evening during busier times of the year. His parents report that he has had fever since the early morning with temperatures of 38° C measured on 2 occasions. He has not been feeding well. He has not been in contact with sick people.

He is up to date with vaccination. He has not received a vaccination in the last 48 hours.

His axillary temperature is 38.6° C, heart rate: 140/ min, respiratory rate 40/min. He appears well, he is alert, has warm extremities, and the rest of the physical examination is normal. There is no clear focus of infection.

C01 What do you think is the probability that he has a bacterial infection? TICK ONE BOX

□ I don't know

□ ≥80% probability

□ 60-79% probability

□ 40-59% probability

□ 20-39% probability

□ 10-19% probability

□ <10% probability

C02 In your workplace, would you carry out any available diagnostic test (including blood, urine, respiratory, or other tests) in this patient, as part of your initial assessment? TICK ONE BOX

In this question, we are interested in both rapid point-of-care tests and hospital lab-based tests

□ Yes **GO TO QUESTION C03**

□ No **GO TO QUESTION C09**

C03 Would you prescribe antibiotics? TICK ONE BOX

□ Yes, definitely

□ No, definitely

□ It will depend on the diagnostic test results

C04 Would you admit the patient? TICK ONE BOX

□ Yes, definitely

□ No, definitely

□ It will depend on the diagnostic test results

How important to you are the following reasons for carrying out a diagnostic test in this patient? TICK ONE BOX PER ROW

	Not at all important	Slightly important	Moderately important	Important	Fairly important	Very important	Absolutely essential
C05 **To help deciding whether to prescribe antibiotics**	□	□	□	□	□	□	□
C06 **To help deciding whether to admit the patient**	□	□	□	□	□	□	□
C07 **To help deciding whether the patient needs urgent medical assessment or can be reassessed later on**	□	□	□	□	□	□	□
C08 **To reassure parents**	□	□	□	□	□	□	□

GO TO SECTION D

C09 Would you prescribe antibiotics? TICK ONE BOX

□ Yes

□ No

C10 Would you observe, admit or discharge the patient? TICK ONE BOX

□ I would observe the patient for a few hours

□ I would admit the patient to the inpatient ward

□ I would discharge the patient

C11 Why would you NOT use diagnostic tests in this patient as part of your initial assessment? TICK ONE BOX

□ Tests that I would like to use are not available **GO TO QUESTION C12**

□ Tests would not change my clinical management **GO TO SECTION D**

□ I would first observe the patient for few hours **GO TO SECTION D**

□ **Other, please specify**

AND GO TO SECTION D

C12 Assuming all the following tests are available in your workplace, please indicate which test you would use in this clinical scenario, and which version (POCT and/or lab version). TICK ONE BOX PER ROW

DIAGNOSTIC TESTS	I would not use this test	I would use the POCT version	I would use the lab version	I would use both the POCT and lab versions
C12.1 **C-Reactive protein**	□	□	□	□
C13 **Procalcitonin**	□	□	□	□
C14 **Full blood cell count or white blood cell count**	□	□	□	□
C15 **Blood gas (with or without lactate)**	□	□	□	□
C16 **Lactate alone**	□	□	□	□
C16.2 **Blood culture**	□		□	
C17 **Urine microscopy and/or nitrites**	□	□	□	□
C18 **Urine culture and sensitivity**	□		□	
C19 **Urine dipstick**	□	□	□ Urine dipstick are sometime done in the lab	□
C20 **Influenza**	□	□	□	□
C21 **Respiratory Syncytial Virus**	□	□	□	□

C21.2 **CSF metrics, culture, sensitivity (+- PCR for herpes simplex or other viruses)**	□		□	

C22 Other tests. Please specify:

SECTION D: PREFERENCE OF RAPID POCTS VS LAB TESTS, AND CHARACTERISTICS OF FUTURE TESTS

In the following section, we are interested in your opinion about using laboratory tests versus rapid point-of- care tests in general, i.e. NOT specifically related to the clinical scenario described earlier. We will use C-reactive protein (CRP) as an example.

D01 Do you think C-reactive protein has any role in the management of children with a suspicion of infection? TICK ONE BOX

□ Yes **GO TO QUESTION D02**

□ No **GO TO QUESTION D03**

D02 If both rapid point-of-care and laboratory versions of C-reactive protein were available, which version would you prefer generally? TICK ONE BOX

□ I would prefer the rapid point-of-care version

□ I would prefer the laboratory version

□ I would use both tests

□ I do not know

The next three questions are about your opinion about the need for new <u>blood-based</u> diagnostic tests for the management of children with acute infection.

D03 Do you think new tests are needed? TICK ONE BOX

□ Yes **GO TO QUESTION D04**

□ No **GO TO QUESTION D13**

D04 How important to you would be the following purposes of the new tests?

TICK ONE BOX PER ROW

	Not at all important	Slightly important	Moderately important	Important	Fairly important	Very important	Absolutely essential
D04.1 **To predict risk of developing severe disease**	□	□	□	□	□	□	□

(regardless of causative pathogen)							
D05 **To indicate the presence/absence of any bacterial infection**	□	□	□	□	□	□	□
D06 **To identify specific bacterial infections**	□	□	□	□	□	□	□
D07 **To indicate sensitivity to antibiotics**	□	□	□	□	□	□	□
D08 **To indicate the presence/absence of any viral infection**	□	□	□	□	□	□	□

D09 Are there other purposes that are important to you? TICK ONE BOX

□ No

□ Yes

D10 If Yes, specify:

D11 What is the maximum time to get results beyond which you would not want to use the new tests?

D12 If a new finger prick test became available that differentiates bacterial from viral infections with high sensitivity and specificity and reasonable cost, how willing would you be to use the test? TICK ONE BOX

□ I would be among the first to want to use it

□ I would use it but only after few of my peers used it

□ I would want to use it if it became common practice

□ I am unlikely to use such a test

□ I don't know

S3 Supplementary Materials: additional explanations of the multilevel regression modelling

Multilevel logistic regressions are useful because they allow separation of the effect, on the outcome of interest, of specific characteristics of individual observations from the effect of a setting or context, that is shared by several observations (often called 'clusters'). We used the mixed-effects approach developed by Merlo and colleagues, based on the stepwise use of fixed effects to measure the effect of specific characteristics, and random effects to measure the effect of a setting/context.

Multilevel analysis to identify determinants of the availability of POCTs

In the analysis to identify determinants of the availability of POCTs, each workplace (primary care practice or hospital) is an individual observation. Each observation has specific characteristics that vary between observations (for example some hospitals are private, while others are public). Each cluster (in this study, each country) share many common characteristics, some measured (i.e., health expenditure per capita, and main financing scheme) but many unmeasured (for example laws regulating the use of commercial advertisement to promote POCTs, or national clinical guidelines). The country characteristics are the same for all observations from the same country.

To separate the effect on the availability of POCTs of specific workplace characteristics from the effect of country as a whole, we used the following mixed-effects stepwise approach: In Model 1, specific workplace characteristics were analysed using fixed effects. This model is a base that was used as a comparator of Model 2. In Model 2 we added a second level of analysis, the country of work, as a random effect (Table IV). One of the benefits of a random effect is that it allows incorporating both measured and unmeasured country characteristics. It also allows the country of work to vary while the workplace characteristics are fixed, which in turn allows understanding of the relative contributions of workplace characteristics and of country as a whole to the availability of POCTs. We assessed these contributions through the change in the area under the receiver operating characteristic curve (AUC) and the median odds ratio (MOR). The change in AUC between models 1 and 2 quantifies the added value of having information on the country as a whole when it comes to identifying the

availability of POCTs. The MOR quantifies the magnitude of the random effect variance of country as a whole. The MOR is the median value of the distribution of ORs obtained when randomly picking two workplaces with the same characteristics from two different countries and comparing the one with the higher availability of POCT to the one with the lower availability. If the MOR= 1, this means that there is no variation in the outcome across countries. If the MOR> 1, there is variation across countries, and the larger the MOR the larger the variation is.

In Model 3, we sought to identify characteristics through which the country effect as a whole occurs by adding specific measured country characteristics to the model. As in models 1 and 2, the workplace characteristics were used as fixed effects, to which we added two measured country characteristics, health expenditure per capita and main financing scheme (also as fixed effects), while keeping the remaining unmeasured country characteristics as random effects. We used the 80% interval odds ratio (IOR80) to measure the fixed effects of the country characteristics. Using traditional odd ratios (ORs) for variables varying on the cluster level is incorrect, because in this case ORs only allow comparison of workplaces within a cluster (the country) but not across clusters. The IOR80 overcomes this limitation. The IOR80 is defined as the middle 80% range of the distribution of ORs formed by making random pairwise comparisons between workplaces with identical characteristics but differing on one of the country-specific characteristics (an example of this would be a comparison between a workplace from a country where the main financing scheme is through government funding, with another workplace that is identical except that it is located in a country where the financing scheme is through social health insurance). The IOR80 interval is narrow if the between-country variability is small, and it is wide if the between-country variability is large. If the IOR80 interval contains one, the variability of the country as a whole is large in comparison with the effect of the country characteristic, and the effect of the country characteristic is considered as minor. If the IOR does not contain one, then the effect of the country characteristic is large in comparison with the variability of the country as a whole, and the country characteristic is considered as important. Model 3 was also used to assess the effect of workplace characteristics adjusting for county as a whole for the two measured country characteristics, as these combined adjustments were not done in Models 1 and 2.

All the variables considered in these analyses were identified through direct acyclic graph (see section 4).

Table IV. The three models for the multilevel regression analysis on the availability of POCTs

	Model 1	**Model 2**	**Model 3**
Purpose	Base model to be used as a comparator when assessing the effect of adding country as a whole	To assess the effect of adding country as a whole to Model 1. This allows assessment of the effect of workplace characteristics, and of country as a whole to the availability of POCTs	1.To assess the effect of country specific characteristics. 2.To assess the effect of workplace characteristics adjusted for country as a whole and for country specific characteristics
Measure of assessment	-	1. Change in area under the curve 2. Median odds ratios	1. 80% interval odds ratios (for country characteristics) 2. Odds ratios (for workplace characteristics)
Analysis of primary care practices			
Levels			
Workplace (Primary care practice)	X	X	X
Country of work		X	X
Primary care practice characteristics			
Sector of activity (private/public)	X	X	X

Practice size (solo/ group practice)	X	X	X
Turnaround time for diagnostics results from the external laboratory (continuous)	X	X	X
Distance to this laboratory (continuous)	X	X	X
Who takes bloods (doctor/another person)	X	X	X
Country characteristics			
Health expenditure per capita (continuous)			X
Main financing scheme (government/mandatory social health insurance/voluntary insurance or out-of-pocket)			X
Analysis of hospitals			
Levels			
Workplace (hospital)	X	X	X
Country of work		X	X
Hospital characteristics			
Sector of activity (private/public)	X	X	X
Level of care (secondary/tertiary hospital),	X	X	X
Hospital specialty (general	X	X	X

hospital/paediatric or mother and child hospital)			
Hospital lab turnaround time for routine tests (continuous)	X	X	X
Who takes bloods (doctor/another person	X	X	X
Country characteristics			
Health expenditure per capita (continuous)			X
Main financing scheme (government/mandatory social health insurance/voluntary insurance or out-of-pocket)			X

Multilevel analysis to identify determinants of the use of POCTs in the clinical scenario

We used a similar approach for the multilevel analyses to identify determinants of the use of each POCT in the clinical scenario except that we used only two models instead of three (Table V). Model 4 was similar to Model 1, except that it included workplace and clinician characteristics (not only workplace characteristics), as we considered that clinicians' characteristics are important in the decision to use a diagnostic. We kept workplace and clinician characteristics as a single level, because most workplaces had only one clinician participating in the survey. To use an additional level for clinician characteristics, we would have needed several clinicians for most workplaces. Model 5 was similar to Model 2. We did not have a third model in which we would have assessed the effect of country characteristics on the outcome, because the two measured country characteristics we used in Model 3 were not considered relevant to the decision made by a clinician to use a POCT.

The workplace characteristics were the same as in Models 1, 2 and 3. The clinician characteristics in primary care were: years of clinical practice (continuous) and average consultation time (continuous). In hospitals we added clinical expertise (general paediatrician/trainee/specialist paediatrician) to these two characteristics (Table V).

Table V. The two models for the multilevel analysis on the use of POCTs in the clinical scenario

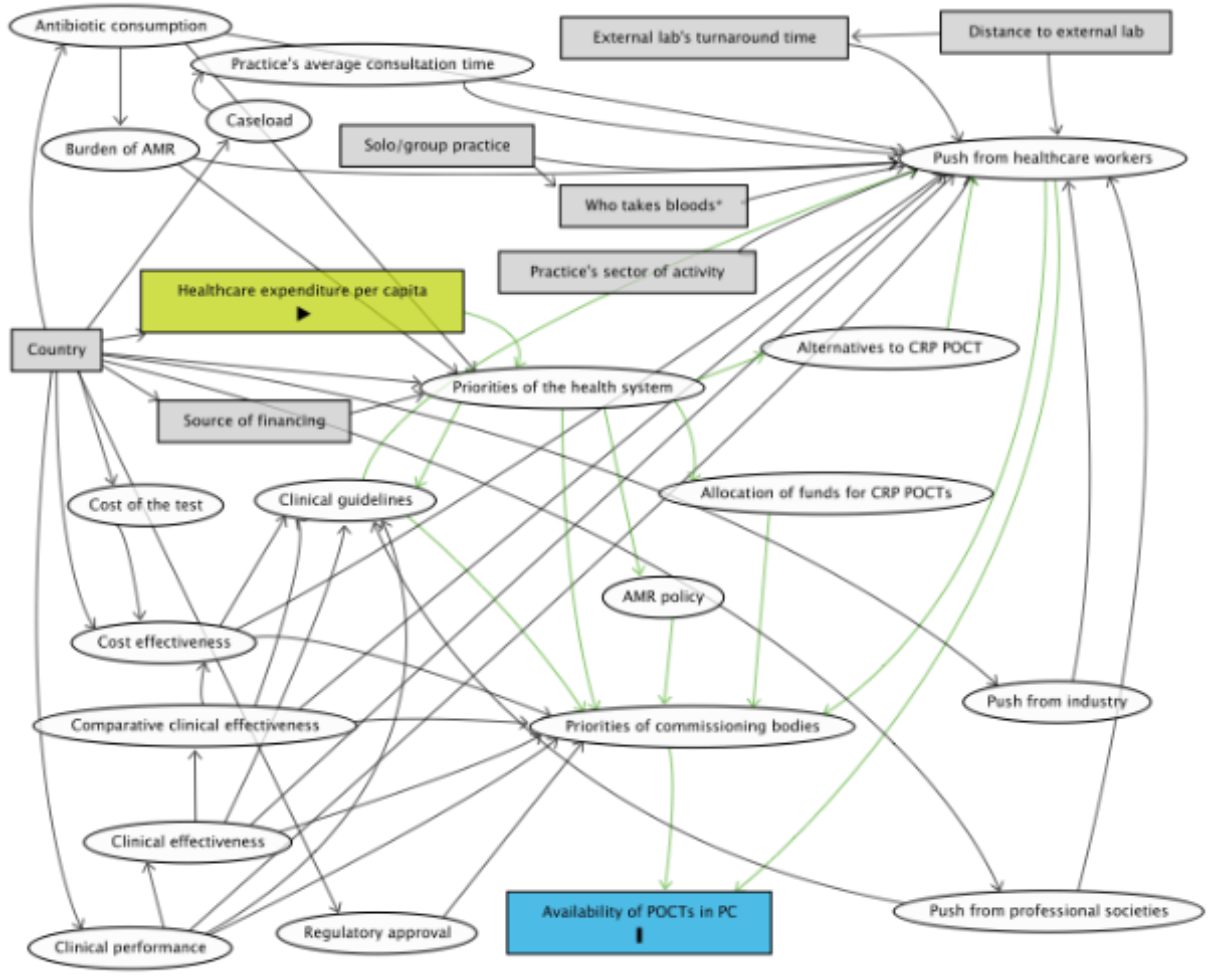
	Model 4	**Model 5**
Purpose	Base model to be used as a comparator when assessing the effect of adding country as a whole	To assess the effect of adding country as a whole to Model 4. This allows assessment of the effect of workplace and clinician characteristics, and of country as a whole on the use of POCTs
Measure of assessment	-	1. Change in area under the curve 2. Median odds ratios 3. Odds ratios
Analysis of primary care practices		
Levels		
Workplace (Primary care practice)	X	X
Country of work		X
Clinicians and primary care practice characteristics		
Years of clinical practice (continuous)	X	X
Average consultation time (continuous)	X	X
Sector of activity (private/public)	X	X
Practice size (solo/ group practice)	X	X

Turnaround time for diagnostics results from the external laboratory (continuous)	X	X
Distance to this laboratory (continuous)	X	X
Who takes bloods (doctor/another person)	X	X
Analysis of hospitals		
Levels		
Workplace (hospital)	X	X
Country of work		X
Clinicians and hospital characteristics		
Years of clinical practice (continuous)	X	X
Clinical expertise (general paediatrician/trainee/specialist paediatrician)	X	X
Average consultation time (continuous)	X	X
Sector of activity (private/public)	X	X
Level of care (secondary/tertiary hospital)	X	X
Hospital specialty (general hospital/paediatric or mother and child hospital)	X	X
Hospital lab turnaround time for routine tests (continuous)	X	X
Who takes bloods (doctor/another person	X	X

S4 Supplementary Materials: directed acyclic graphs for the inclusion of explanatory variable in the regression models

We used the directed acyclic graphs approach to choose which covariates to include in the multilevel analyses to minimize the magnitude of the bias in the estimate produced.

Availability of POCTs in primary care



Green box: main explanatory variable

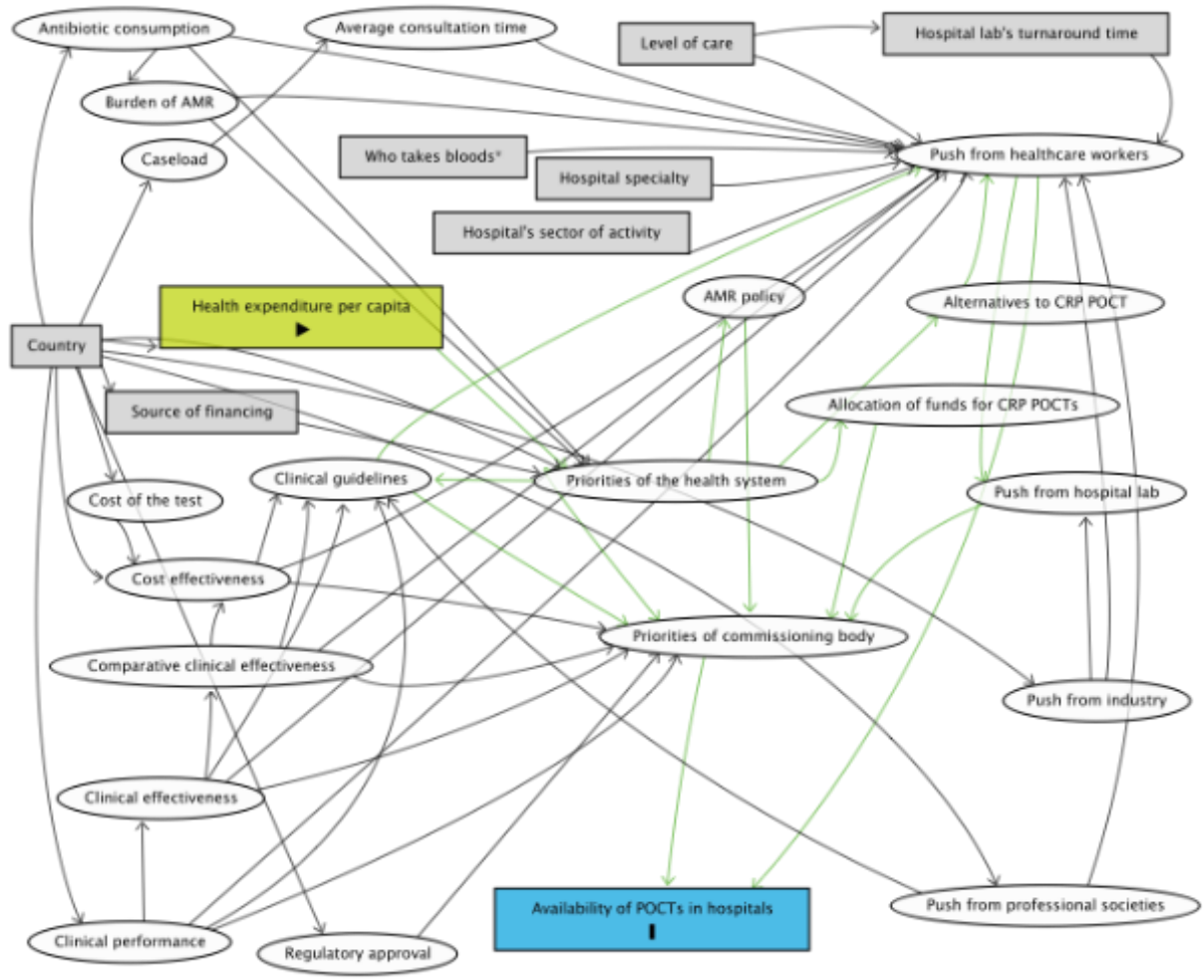
Blue box: outcome

Grey boxes: measured explanatory variables

White boxes: unmeasured explanatory variables

*except for UD, GAS, RSV, and influenza POCTS

Availability of POCTs in hospitals



Green box: main explanatory variable

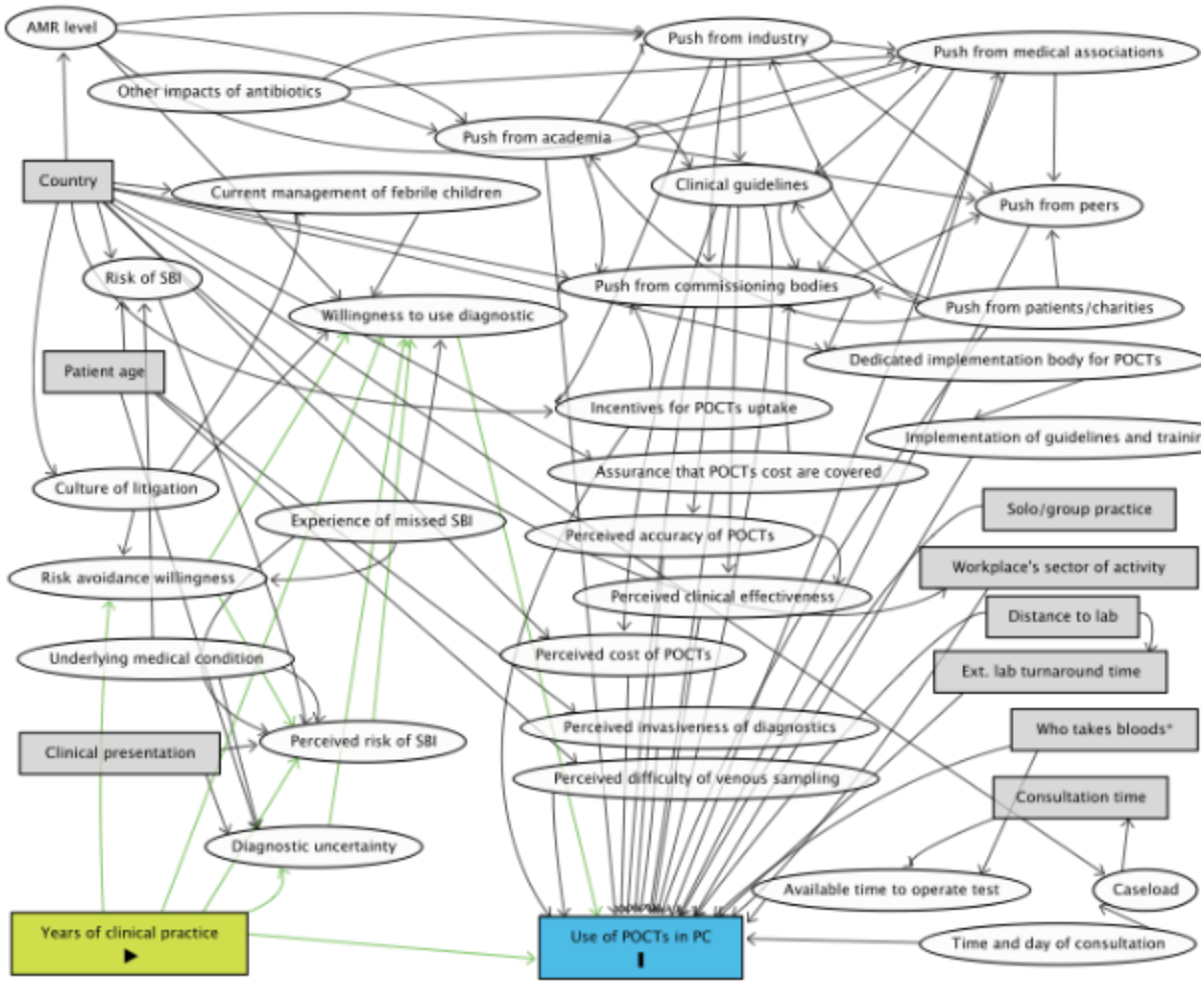
Blue box: outcome

Grey boxes: measured explanatory variables

White boxes: unmeasured explanatory variables

*except for UD, GAS, RSV, and influenza POCTS

Use of POCTs in an infant with undifferentiated fever in primary care



Green box: main explanatory variable

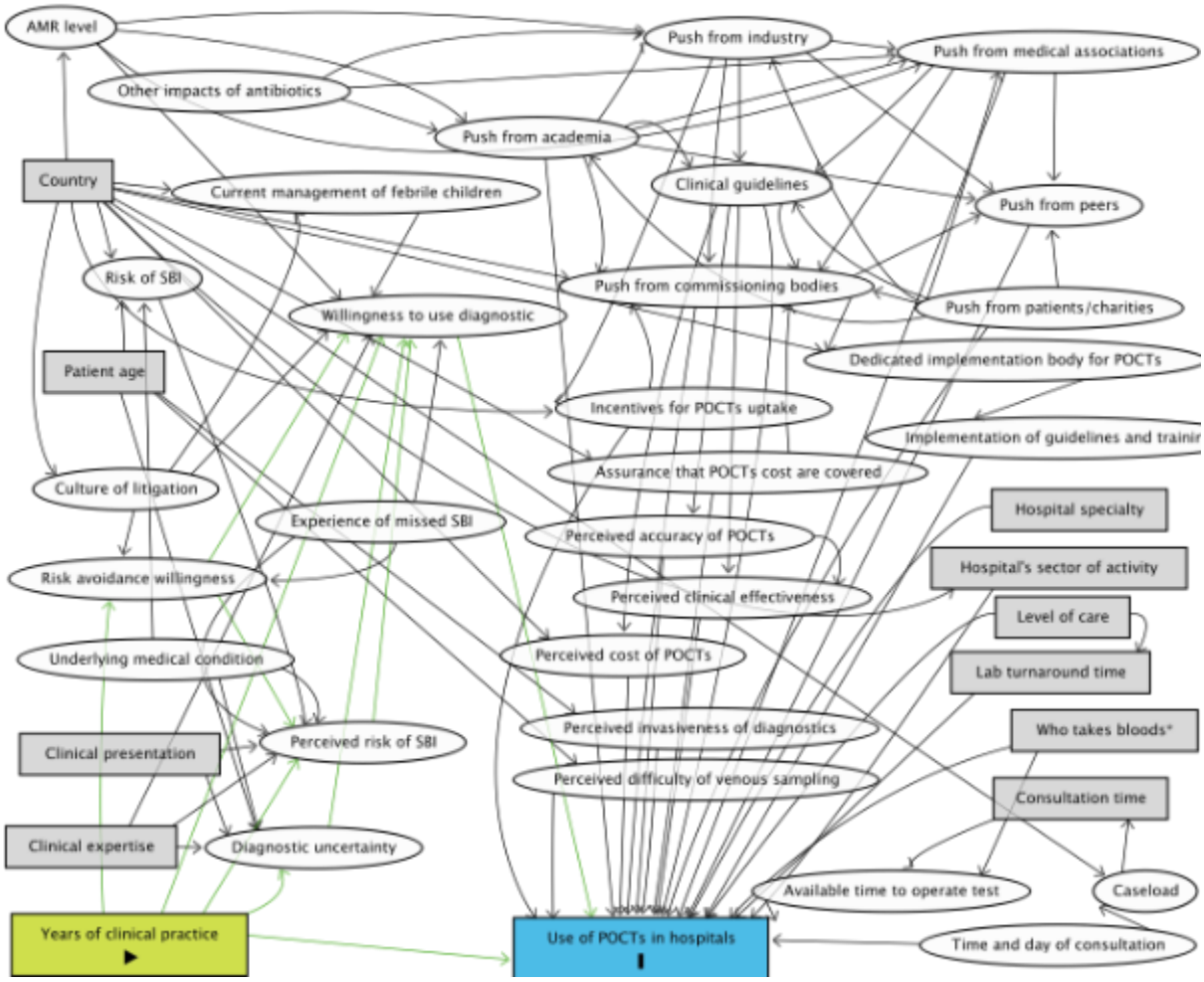
Blue box: outcome

Grey boxes: measured explanatory variables

White boxes: unmeasured explanatory variables

*except for UD, GAS, RSV, and influenza POCTS

Use of POCTs in an infant with undifferentiated fever in hospitals



Green box: main explanatory variable

Blue box: outcome

Grey boxes: measured explanatory variables

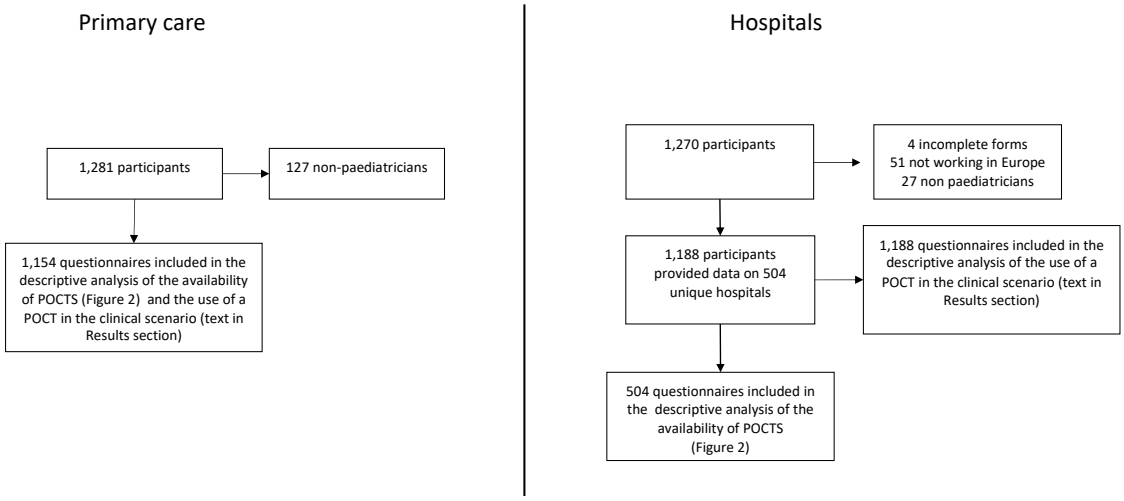
White boxes: unmeasured explanatory variables

*except for UD, GAS, RSV, and influenza POCTS

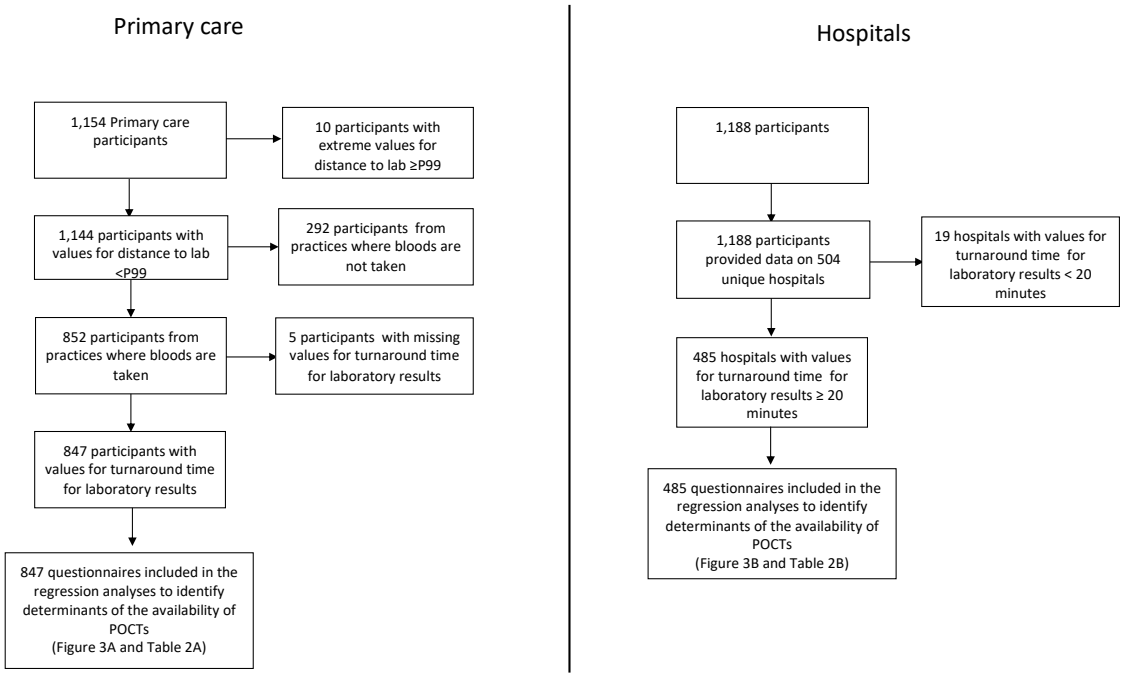
S5 Supplementary Materials: flow diagram of included observations per analysis

Only questionnaires that provided data on the outcomes and potential explanatory variables were included in the analysis. The number of questionnaires that were excluded and the reasons for exclusion are summarised below:

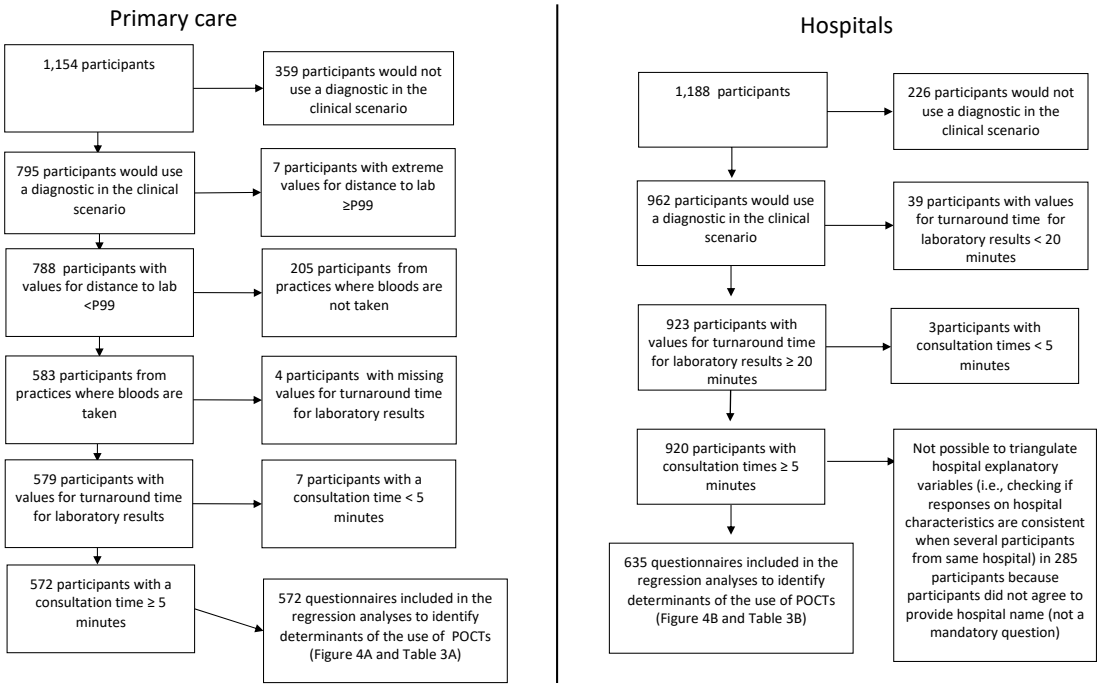
Inclusion of questionnaires in the descriptive analyses



Inclusion of questionnaires in the analyses to identify determinants of the availability of POCTs



Inclusion of questionnaires in the analyses to identify determinants of the use of POCTs use



S6 Supplementary Materials: availability of POCTs per country

Primary care

Country	**Urine Dipstick**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.986	0.926	1.000
Belgium	8	0.875	0.473	0.997
Croatia	10	0.700	0.348	0.933
Cyprus	22	0.727	0.498	0.893
Czech Rep.	15	0.867	0.595	0.983
Finland	11	1.000	0.715	1.000
France	156	0.929	0.877	0.964
Germany	98	0.990	0.944	1.000
Greece	63	0.635	0.504	0.753
Hungary	76	1.000	0.953	1.000
Israel	56	0.964	0.877	0.996
Italy	144	0.944	0.893	0.976
Latvia	6	0.667	0.223	0.957
Lithuania	6	0.667	0.223	0.957
Poland	35	0.514	0.340	0.686
Slovenia	88	0.852	0.761	0.919
Spain	173	0.988	0.959	0.999
Switzerland	51	0.980	0.896	1.000
Ukraine	63	0.683	0.553	0.794
Total	154	0.900	0.882	0.917

Country	**GAS**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	

Austria	73	0.904	0.812	0.961
Belgium	8	0.625	0.245	0.915
Croatia	10	0.5	0.187	0.813
Cyprus	22	0.727	0.498	0.893
Czech Rep.	15	1	0.782	1.000
Finland	11	0.818	0.482	0.977
France	156	0.962	0.918	0.986
Germany	98	0.939	0.871	0.977
Greece	63	0.667	0.537	0.780
Hungary	76	0.5	0.383	0.617
Israel	56	0.911	0.804	0.970
Italy	144	0.951	0.902	0.980
Latvia	6	0.833	0.359	0.996
Lithuania	6	0.833	0.359	0.996
Poland	35	0.2	0.084	0.369
Slovenia	88	0.989	0.938	1.000
Spain	173	0.908	0.854	0.946
Switzerland	51	1	0.930	1.000*
Ukraine	63	0.587	0.456	0.710
Total	1154	0.845	0.823	0.865

Country	**RSV**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.151	0.078	0.254
Belgium	8	0.375	0.085	0.755
Croatia	10	0.1	0.003	0.445
Cyprus	22	0.136	0.029	0.349
Czech Rep.	15	0.2	0.043	0.481
Finland	11	0.818	0.482	0.977
France	156	0.237	0.173	0.312
Germany	98	0.122	0.065	0.204
Greece	63	0.159	0.079	0.273

Hungary	76	0.066	0.022	0.147
Israel	56	0.018	0.000	0.096
Italy	144	0.076	0.039	0.133
Latvia	6	0.167	0.004	0.641
Lithuania	6	0	0.000	0.459
Poland	35	0.029	0.001	0.149
Slovenia	88	0.159	0.090	0.252
Spain	173	0.04	0.016	0.082
Switzerland	51	0.529	0.385	0.671
Ukraine	63	0.127	0.056	0.235
Total	1154	0.142	0.122	0.164

Country	**Influenza**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.301	0.199	0.420
Belgium	8	0.375	0.085	0.755
Croatia	10	0.1	0.003	0.445
Cyprus	22	0.455	0.244	0.678
Czech Rep.	15	0.133	0.017	0.405
Finland	11	0.909	0.587	0.998
France	156	0.397	0.320	0.479
Germany	98	0.286	0.199	0.386
Greece	63	0.333	0.220	0.463
Hungary	76	0.066	0.022	0.147
Israel	56	0.071	0.020	0.173
Italy	144	0.167	0.110	0.238
Latvia	6	0.333	0.043	0.777
Lithuania	6	0.5	0.118	0.882
Poland	35	0.114	0.032.	0.267
Slovenia	88	0.284	0.193	0.390
Spain	173	0.092	0.054	0.146
Switzerland	51	0.549	0.403	0.689

Ukraine	63	0.603	0.472	0.724
Total	1154	0.267	0.242	0.293

Country	**CRP**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.945	0.866	0.985
Belgium	8	0.375	0.085	0.755
Croatia	10	0.700	0.348	0.933
Cyprus	22	0.500	0.282	0.718
Czech Rep.	15	1.000	0.782	1.000
Finland	11	0.818	0.482	0.977
France	156	0.468	0.388	0.549
Germany	98	0.765	0.669	0.845
Greece	63	0.222	0.127	0.345
Hungary	76	0.737	0.623	0.831
Israel	56	0.286	0.173	0.422
Italy	144	0.444	0.362	0.529
Latvia	6	0.333	0.043	0.777
Lithuania	6	0.833	0.359	0.996
Poland	35	0.200	0.084	0.369
Slovenia	88	0.784	0.684	0.865
Spain	173	0.139	0.091	0.199
Switzerland	51	0.941	0.838	0.988
Ukraine	63	0.413	0.290	0.544
Total	1154	0.514	0.485	0.543

Country	**Procalcitonin**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.068	0.023	0.153

Belgium	8	0.125	0.003	0.527
Croatia	10	0.1	0.003	0.445
Cyprus	22	0.136	0.029	0.349
Czech Rep.	15	0.267	0.078	0.551
Finland	11	0.182	0.023	0.518
France	156	0.006	0.000	0.035
Germany	98	0.01	0.000	0.056
Greece	63	0.032	0.004	0.110
Hungary	76	0.013	0.000	0.071
Israel	56	0.071	0.020	0.173
Italy	144	0.049	0.020	0.098
Latvia	6	0.333	0.043	0.777
Lithuania	6	0	0.000	0.459
Poland	35	0.086	0.018	0.231
Slovenia	88	0.057	0.019	0.128
Spain	173	0.087	0.049	0.139
Switzerland	51	0.137	0.057	0.263
Ukraine	63	0.222	0.127	0.345
Total	1154	0.068	0.054	0.084

Country	**Full blood count**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.89	0.795	0.951
Belgium	8	0.25	0.032	0.651
Croatia	10	0.6	0.262	0.878
Cyprus	22	0.318	0.139	0.549
Czech Rep.	15	0.133	0.017	0.405
Finland	11	0.818	0.482	0.977
France	156	0.026	0.007	0.064
Germany	98	0.469	0.368	0.573
Greece	63	0.19	0.102	0.309
Hungary	76	0.158	0.084	0.260

Israel	56	0.286	0.173	0.422
Italy	144	0.146	0.093	0.214
Latvia	6	0.333	0.043	0.777
Lithuania	6	0.833	0.359	0.996
Poland	35	0.571	0.394	0.737
Slovenia	88	0.727	0.622	0.817
Spain	173	0.191	0.135	0.257
Switzerland	51	0.804	0.669	0.902
Ukraine	63	0.667	0.537	0.780
Total	1154	0.354	0.327	0.383

Country	**Blood gas analysis (with or without lactate)**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.055	0.015	0.134
Belgium	8	0.125	0.003	0.527
Croatia	10	0.1	0.003	0.445
Cyprus	22	0.045	0.001	0.228
Czech Rep.	15	0.2	0.043	0.481
Finland	11	0.182	0.023	0.518
France	156	0.071	0.036	0.123
Germany	98	0.051	0.017	0.115
Greece	63	0.079	0.026	0.176
Hungary	76	0.066	0.022	0.147
Israel	56	0.036	0.004	0.123
Italy	144	0.056	0.024	0.107
Latvia	6	0.333	0.043	0.777
Lithuania	6	0	0.000	0.459
Poland	35	0.429	0.263	0.606
Slovenia	88	0.068	0.025	0.143
Spain	173	0.052	0.024	0.096
Switzerland	51	0.098	0.033	0.214
Ukraine	63	0.175	0.091	0.291

Total	1154	0.083	0.068	0.101

Country	**Lactate**			
	Number of primary care practices	Proportion with POCT available	[95% Conf. Interval]	
Austria	73	0.068	0.023	0.153
Belgium	8	0.25	0.032	0.651
Croatia	10	0	0.000	0.308
Cyprus	22	0.045	0.001	0.228
Czech Rep.	15	0	0.000	0.218
Finland	11	0.091	0.002	0.413
France	156	0.045	0.018	0.090
Germany	98	0.02	0.002	0.072
Greece	63	0.032	0.004	0.110
Hungary	76	0.066	0.022	0.147
Israel	56	0.107	0.040	0.219
Italy	144	0.042	0.015	0.088
Latvia	6	0.333	0.043	0.777
Lithuania	6	0	0.000	0.459
Poland	35	0.114	0.032	0.267
Slovenia	88	0.102	0.048	0.185
Spain	173	0.029	0.009	0.066
Switzerland	51	0.078	0.022	0.189
Ukraine	63	0.143	0.067	0.254
Total	1154	0.061	0.076	

Hospitals

Country	**Urine dipstick**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	1.000	0.884	1.000

Belgium	40	0.875	0.732	0.958
Bulgaria	3	0.667	0.094	0.992
Croatia	13	0.923	0.640	0.998
Cyprus	3	1.000	0.292	1.000
Czech Rep.	1	1.000	0.025	1.000
Denmark	3	1.000	0.292	1.000
Finland	12	1.000	0.735	1.000
France	46	0.978	0.885	0.999
Germany	43	0.907	0.779	0.974
Greece	29	0.862	0.683	0.961
Hungary	12	1.000	0.735	1.000
Ireland	4	1.000	0.398	1.000
Israel	4	1.000	0.398	1.000
Italy	20	1.000	0.832	1.000
Latvia	4	1.000	0.398	1.000
Lithuania	3	0.333	0.008	0.906
Malta	3	1.000	0.292	1.000
The Netherlands	27	0.667	0.460	0.835
Norway	23	1.000	0.852	1.000
Poland	11	0.545	0.234	0.833
Portugal	23	1.000	0.852	1.000
Romania	6	1.000	0.541	1.000
Slovenia	7	0.571	0.184	0.901
Spain	50	0.980	0.894	0.999
Sweden	8	1.000	0.631	1.000
Switzerland	11	1.000	0.715	1.000
Ukraine	27	0.741	0.537	0.889
United Kingdom	38	1.000	0.907	1.000
Total	504	0.915	0.887	0.938

Country	**GAS**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.900	0.735	0.979

Belgium	40	0.550	0.385	0.707
Bulgaria	3	0.667	0.094	0.992
Croatia	13	0.538	0.251	0.808
Cyprus	3	0.667	0.094	0.992
Czech Rep.	1	1.000	0.025	1.000
Denmark	3	0.667	0.094	0.992
Finland	12	0.917	0.615	0.998
France	46	0.978	0.885	0.999
Germany	43	0.651	0.491	0.790
Greece	29	0.828	0.642	0.942
Hungary	12	0.167	0.021	0.484
Ireland	4	0	0.000	0.602
Israel	4	0.250	0.006	0.806
Italy	20	0.650	0.408	0.846
Latvia	4	0.500	0.068	0.932
Lithuania	3	0.667	0.094	0.992
Malta	3	0.667	0.094	0.992
The Netherlands	27	0.074	0.009	0.243
Norway	23	0.870	0.664	0.972
Poland	11	0.636	0.308	0.891
Portugal	23	0.783	0.563	0.925
Romania	6	0.667	0.223	0.957
Slovenia	7	1.000	0.590	1.000
Spain	50	0.900	0.782	0.967
Sweden	8	1.000	0.631	1.000
Switzerland	11	1.000	0.715	1.000
Ukraine	27	0.481	0.287	0.681
United Kingdom	38	0.026	0.001	0.138
Total	504	0.653	0.609	0.694

Country	**RSV**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.767	0.577	0.901

Belgium	40	0.75	0.588	0.873
Bulgaria	3	0.333	0.008	0.906
Croatia	13	0.615	0.316	0.861
Cyprus	3	0	0.000	0.708
Czech Rep.	1	1	0.025	1.000
Denmark	3	0.667	0.094	0.992
Finland	12	0.75	0.428	0.945
France	46	0.37	0.232	0.525
Germany	43	0.767	0.614	0.882
Greece	29	0.517	0.325	0.706
Hungary	12	0.417	0.152	0.723
Ireland	4	0.25	0.006	0.806
Israel	4	0	0.000	0.602
Italy	20	0.35	0.154	0.592
Latvia	4	0.25	0.006	0.806
Lithuania	3	0	0.000	0.708
Malta	3	0.333	0.008	0.906
The Netherlands	27	0.63	0.424	0.806
Norway	23	0.565	0.345	0.768
Poland	11	0.818	0.482	0.977
Portugal	23	0.522	0.306	0.732
Romania	6	0.5	0.118	0.882
Slovenia	7	0.571	0.184	0.901
Spain	50	0.88	0.757	0.955
Sweden	8	0.75	0.349	0.968
Switzerland	11	0.818	0.482	0.977
Ukraine	27	0.148	0.042	0.337
United Kingdom	38	0.289	0.154	0.459
Total	504	0.567	0.523	0.611

Country	**Influenza**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.800	0.614	0.923

Belgium	40	0.750	0.588	0.873
Bulgaria	3	0.667	0.094	0.992
Croatia	13	0.538	0.251	0.808
Cyprus	3	0.333	0.008	0.906
Czech Rep.	1	1.000	0.025	1.000
Denmark	3	0.667	0.094	0.992
Finland	12	0.750	0.428	0.945
France	46	0.652	0.498	0.786
Germany	43	0.651	0.491	0.790
Greece	29	0.552	0.357	0.736
Hungary	12	0.167	0.021	0.484
Ireland	4	0.250	0.006	0.806
Israel	4	0.000	0.000	0.602
Italy	20	0.100	0.012	0.317
Latvia	4	0.500	0.068	0.932
Lithuania	3	0.333	0.008	0.906
Malta	3	0.333	0.008	0.906
The Netherlands	27	0.741	0.537	0.889
Norway	23	0.522	0.306	0.732
Poland	11	0.636	0.308	0.891
Portugal	23	0.522	0.306	0.732
Romania	6	0.667	0.223	0.957
Slovenia	7	0.571	0.184	0.901
Spain	50	0.840	0.709	0.928
Sweden	8	0.750	0.349	0.968
Switzerland	11	0.727	0.390	0.940
Ukraine	27	0.519	0.319	0.713
United Kingdom	38	0.316	0.175	0.487
Total	504	0.595	0.551	0.638

Country	**CRP**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.900	0.735	0.979

Belgium	40	0.300	0.166	0.465
Bulgaria	3	0.667	0.094	0.992
Croatia	13	0.615	0.316	0.861
Cyprus	3	0.333	0.008	0.906
Czech Rep.	1	1.000	0.025	1.000
Denmark	3	0.667	0.094	0.992
Finland	12	0.833	0.516	0.979
France	46	0.370	0.232	0.525
Germany	43	0.349	0.210	0.509
Greece	29	0.724	0.528	0.873
Hungary	12	0.583	0.277	0.848
Ireland	4	0.000	0.000	0.602
Israel	4	0.250	0.006	0.806
Italy	20	0.350	0.154	0.592
Latvia	4	0.250	0.006	0.806
Lithuania	3	0.667	0.094	0.992
Malta	3	0.333	0.008	0.906
The Netherlands	27	0.185	0.063	0.381
Norway	23	0.348	0.164	0.573
Poland	11	0.545	0.234	0.833
Portugal	23	0.522	0.306	0.732
Romania	6	0.833	0.359	0.996
Slovenia	7	0.143	0.004	0.579
Spain	50	0.700	0.554	0.821
Sweden	8	1.000	0.631	1.000
Switzerland	11	0.455	0.167	0.766
Ukraine	27	0.519	0.319	0.713
United Kingdom	38	0.053	0.006	0.177
Total	504	0.468	0.424	0.513

Country	**Procalcitonin**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.367	0.199	0.561

Belgium	40	0.075	0.016	0.204
Bulgaria	3	0	0.000	0.708
Croatia	13	0.385	0.139	0.684
Cyprus	3	0.333	0.008	0.906
Czech Rep.	1	1	0.025	1.000
Denmark	3	0	0.000	0.708
Finland	12	0.167	0.021	0.484
France	46	0.174	0.078	0.314
Germany	43	0.256	0.135	0.412
Greece	29	0.241	0.103	0.435
Hungary	12	0.417	0.152	0.723
Ireland	4	0	0.000	0.602
Israel	4	0	0.000	0.602
Italy	20	0.2	0.057	0.437
Latvia	4	0.25	0.006	0.806
Lithuania	3	0.333	0.008	0.906
Malta	3	0.333	0.008	0.906
The Netherlands	27	0	0.000	0.128
Norway	23	0.13	0.028	0.336
Poland	11	0.545	0.234	0.833
Portugal	23	0.174	0.050	0.388
Romania	6	0.333	0.043	0.777
Slovenia	7	0	0.000	0.410
Spain	50	0.62	0.472	0.753
Sweden	8	0.25	0.032	0.651
Switzerland	11	0.091	0.002	0.413
Ukraine	27	0.407	0.224	0.612
United Kingdom	38	0.026	0.001	0.138
Total	504	0.242	0.205	0.282

Country	**Full blood count**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.767	0.577	0.901

Belgium	40	0.25	0.127	0.412
Bulgaria	3	1	0.292	1.000
Croatia	13	0.692	0.386	0.909
Cyprus	3	0.667	0.094	0.992
Czech Rep.	1	1	0.025	1.000
Denmark	3	0	0.000	0.708
Finland	12	0.75	0.428	0.945
France	46	0.152	0.063	0.289
Germany	43	0.395	0.250	0.556
Greece	29	0.69	0.492	0.847
Hungary	12	0.417	0.152	0.723
Ireland	4	0.25	0.006	0.806
Israel	4	0.25	0.006	0.806
Italy	20	0.25	0.087	0.491
Latvia	4	0.25	0.006	0.806
Lithuania	3	0.667	0.094	0.992
Malta	3	0.333	0.008	0.906
The Netherlands	27	0.111	0.024	0.292
Norway	23	0.304	0.132	0.529
Poland	11	0.545	0.234	0.833
Portugal	23	0.522	0.306	0.732
Romania	6	1	0.541	1.000
Slovenia	7	0	0.000	0.410
Spain	50	0.7	0.554	0.821
Sweden	8	0.375	0.085	0.755
Switzerland	11	0.091	0.002	0.413
Ukraine	27	0.778	0.577	0.914
United Kingdom	38	0.105	0.029	0.248
Total	504	0.427	0.383	0.471

Country	**Blood gas (with or without lactate)**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.967	0.828	0.999

Belgium	40	0.775	0.615	0.892
Bulgaria	3	1	0.292	1.000
Croatia	13	0.769	0.462	0.950
Cyprus	3	1	0.292	1.000
Czech Rep.	1	1	0.025	1.000
Denmark	3	0.333	0.008	0.906
Finland	12	0.75	0.428	0.945
France	46	0.565	0.411	0.711
Germany	43	0.977	0.877	0.999
Greece	29	0.897	0.726	0.978
Hungary	12	0.917	0.615	0.998
Ireland	4	1	0.398	1.000
Israel	4	0.75	0.194	0.994
Italy	20	0.95	0.751	0.999
Latvia	4	0.75	0.194	0.994
Lithuania	3	1	0.292	1.000
Malta	3	1	0.292	1.000
The Netherlands	27	0.667	0.460	0.835
Norway	23	0.957	0.781	0.999
Poland	11	0.636	0.308	0.891
Portugal	23	0.826	0.612	0.950
Romania	6	0.833	0.359	0.996
Slovenia	7	0.857	0.421	0.996
Spain	50	0.88	0.757	0.955
Sweden	8	1	0.631	1.000
Switzerland	11	1	0.715	1.000
Ukraine	27	0.481	0.287	0.681
United Kingdom	38	1	0.907	1.000
Total	504	0.829	0.794	0.861

Country	**Lactate**			
	Number of hospitals	Proportion with POCT available	[95% Conf. Interval]	
Austria	30	0.433	0.255	0.626

Belgium	40	0.35	0.206	0.517
Bulgaria	3	0.333	0.008	0.906
Croatia	13	0.538	0.251	0.808
Cyprus	3	0.667	0.094	0.992
Czech Rep.	1	1	0.025	1.000
Denmark	3	0	0.000	0.708
Finland	12	0.25	0.055	0.572
France	46	0.457	0.309	0.610
Germany	43	0.605	0.444	0.750
Greece	29	0.241	0.103	0.435
Hungary	12	0.5	0.211	0.789
Ireland	4	0.5	0.068	0.932
Israel	4	0.5	0.068	0.932
Italy	20	0.45	0.231	0.685
Latvia	4	0.5	0.068	0.932
Lithuania	3	0.667	0.094	0.992
Malta	3	0.333	0.008	0.906
The Netherlands	27	0.222	0.086	0.423
Norway	23	0.478	0.268	0.694
Poland	11	0.455	0.167	0.766
Portugal	23	0.217	0.075	0.437
Romania	6	0.167	0.004	0.641
Slovenia	7	0	0.000	0.410
Spain	50	0.62	0.472	0.753
Sweden	8	0.375	0.085	0.755
Switzerland	11	0.364	0.109	0.692
Ukraine	27	0.296	0.138	0.502
United Kingdom	38	0.447	0.286	0.617
Total	504	0.417	0.373	0.461

S7 Supplementary Materials: use of POCTs per country

Primary care

Country		Urine dipstick		
		I would not use the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.0102 [.0014,.0701]	0.9898 [.9299,.9986]	1
	Number of participants	1	62	63
Belgium	Proportion (95%CI)	0.1677 [.0232,.6312]	0.8323 [.3688,.9768]	1
	Number of participants	1	6	7
Croatia	Proportion (95%CI)	0.0959 [.0129,.4624]	0.9041 [.5376,.9871]	1
	Number of participants	1	8	9
Cyprus	Proportion (95%CI)	0.08 [.0113,.3989]	0.92 [.6011,.9887]	1
	Number of participants	1	16	17
Czech Re	Proportion (95%CI)	0.1845 [.0505,.4906]	0.8155 [.5094,.9495]	1
	Number of participants	3	9	12

Finland	Proportion (95%CI)	0	1	1
	Number of participants	0	10	10
France	Proportion (95%CI)	0.0712 [.0317,.1521]	0.9288 [.8479,.9683]	1
	Number of participants	6	64	70
Germany	Proportion (95%CI)	0	1	1
	Number of participants	0	59	59
Greece	Proportion (95%CI)	0.2755 [.1653,.422]	0.7245 [.578,.8347]	1
	Number of participants	13	34	47
Hungary	Proportion (95%CI)	0.0831 [.0269,.2292]	0.9169 [.7708,.9731]	1
	Number of participants	3	58	61
Israel	Proportion (95%CI)	0	1	1
	Number of participants	0	18	18
Italy	Proportion (95%CI)	0.0294 [.0091,.0912]	0.9706 [.9088,.9909]	1

	Number of participants	3	108	111
Latvia	Proportion (95%CI)	0	1	1
	Number of participants	0	3	3
Lithuania	Proportion (95%CI)	0.8577 [.3519,.9853]	0.1423 [.0147,.6481]	1
	Number of participants	3	1	4
Poland	Proportion (95%CI)	0.4163 [.2067,.6613]	0.5837 [.3387,.7933]	1
	Number of participants	9	25	34
Slovenia	Proportion (95%CI)	0.2316 [.1389,.3601]	0.7684 [.6399,.8611]	1
	Number of participants	15	53	68
Spain	Proportion (95%CI)	0.0842 [.0405,.1669]	0.9158 [.8331,.9595]	1
	Number of participants	8	118	126
Switzerland	Proportion (95%CI)	0.0218 [.003,.1415]	0.9782 [.8585,.997]	1
	Number of participants	1	31	32
Ukraine	Proportion	0.1534	0.8466	1

	(95%CI)	[.0662,.3164]	[.6836,.9338]	
	Number of participants	8	36	44
Total	Proportion (95%CI)	0.104 [.0813,.1322]	0.896 [.8678,.9187]	1
	Number of participants	76	719	795

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Country		**RSV**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.4563 [.317,.6029]	0.0205 [.005,.0797]	0.1133 [.0339,.3179]	0.4098 [.2815,.5517]	1
	Number of participants	29	2	4	28	63
Belgium	Proportion (95%CI)	0.1994 [.0452,.567]	0.1677 [.0232,.6312]	0.0997 [.0129,.4836]	0.5332 [.1966,.8421]	1
	Number of participants	2	1	1	3	7
Croatia	Proportion (95%CI)	0.5068 [.2082,.8007]	0	0.0959 [.0129,.4624]	0.3973 [.1364,.7334]	1

	Number of participants	5	0	1	3	9
Cyprus	Proportion (95%CI)	0.5183 [.2811,.7476]	0	0.36 [.1635,.6181]	0.1217 [.028,.3997]	1
	Number of participants	9	0	6	2	17
Czech Re.	Proportion (95%CI)	0.6319 [.2179,.9136]	0	0.0531 [.0067,.317]	0.315 [.0556,.7821]	1
	Number of participants	10	0	1	1	12
Finland	Proportion (95%CI)	0.3772 [.1215,.7262]	0	0	0.6228 [.2738,.8785]	1
	Number of participants	5	0	0	5	10
France	Proportion (95%CI)	0.5121 [.3838,.6388]	0	0.0474 [.0106,.1876]	0.4404 [.3152,.5737]	1
	Number of participants	42	0	2	26	70
Germany	Proportion (95%CI)	0.5219 [.3794,.6609]	0.0764 [.0288,.1876]	0.0278 [.0069,.1056]	0.374 [.2398,.5307]	1
	Number of participants	34	4	2	19	59
Greece	Proportion (95%CI)	0.3792 [.2512,.5264]	0.0766 [.0242,.2173]	0.0533 [.0127,.1976]	0.4909 [.3501,.6331]	1
	Number of participants	18	3	2	24	47
Hungary	Proportion	0.3548	0.045	0.0285	0.5718	1

	(95%CI)	[.2171,.5217]	[.0134,.1407]	[.007,.1084]	[.4154,.7149]	
	Number of participants	18	3	2	38	61
Israel	Proportion (95%CI)	0.5549 [.3274,.7614]	0	0	0.4451 [.2386,.6726]	1
	Number of participants	10	0	0	8	18
Italy	Proportion (95%CI)	0.5515 [.4345,.6632]	0.0184 [.0059,.0564]	0.0301 [.0106,.0819]	0.4 [.2915,.5193]	1
	Number of participants	59	3	4	45	111
Latvia	Proportion (95%CI)	1	0	0	0	1
	Number of participants	3	0	0	0	3
Lithuania	Proportion (95%CI)	1	0	0	0	1
	Number of participants	4	0	0	0	4
Poland	Proportion (95%CI)	0.1009 [.022,.3591]	0.0519 [.0094,.2395]	0	0.8472 [.6082,.9519]	1
	Number of participants	4	2	0	28	34
Slovenia	Proportion (95%CI)	0.5084 [.3797,.636]	0.0562 [.0165,.1748]	0.1208 [.0532,.2513]	0.3146 [.2099,.4424]	1
	Number of participants	35	3	6	24	68

Spain	Proportion (95%CI)	0.2989 [.2219,.3894]	0.0297 [.0104,.0819]	0.0226 [.0048,.1001]	0.6487 [.5549,.7323]	1
	Number of participants	42	4	2	78	126
Switzerland	Proportion (95%CI)	0.6674 [.4653,.8223]	0.0218 [.003,.1415]	0.1561 [.0556,.3678]	0.1547 [.0567,.3578]	1
	Number of participants	23	1	4	4	32
Ukraine	Proportion (95%CI)	0.3226 [.1824,.5041]	0.0678 [.027,.16]	0	0.6096 [.4344,.7605]	1
	Number of participants	13	5	0	26	44
Total	Proportion (95%CI)	0.4412 [.402,.4812]	0.0355 [.0243,.0516]	0.0557 [.0386,.0797]	0.4675 [.4274,.5081]	1
	Number of participants	365	31	37	362	795

Country		**Influenza**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.4948 [.3516,.6389]	0.0102 [.0014,.0701]	0.027 [.0061,.1117]	0.4679 [.3297,.6112]	1

	Number of participants	29	1	2	31	63
Belgium	Proportion (95%CI)	0.3671 [.1089,.7336]	0.1677 [.0232,.6312]	0.0997 [.0129,.4836]	0.3655 [.0955,.7587]	1
	Number of participants	3	1	1	2	7
Croatia	Proportion (95%CI)	0.5068 [.2082,.8007]	0	0.0959 [.0129,.4624]	0.3973 [.1364,.7334]	1
	Number of participants	5	0	1	3	9
Cyprus	Proportion (95%CI)	0.36 [.1635,.6181]	0.0391 [.0053,.2371]	0.36 [.1635,.6181]	0.2409 [.088,.5106]	1
	Number of participants	6	1	6	4	17
Czech Rep.	Proportion (95%CI)	0.5005 [.1844,.8162]	0	0.1314 [.0285,.438]	0.3681 [.0864,.7821]	1
	Number of participants	8	0	2	2	12
Finland	Proportion (95%CI)	0.2807 [.0838,.6248]	0	0	0.7193 [.3752,.9162]	1
	Number of participants	4	0	0	6	10
France	Proportion (95%CI)	0.3763 [.2649,.5025]	0	0.0339 [.0048,.2029]	0.5898 [.4609,.7074]	1
	Number of participants	29	0	1	40	70
Germany	Proportion	0.6284	0.0382	0.014	0.3194	1

	(95%CI)	[.4705,.7629]	[.0095,.1411]	[.0019,.0936]	[.1896,.4849]	
	Number of participants	41	2	1	15	59
Greece	Proportion	0.2522	0.0766	0.0576	0.6136	1
	(95%CI)	[.1472,.3972]	[.0242,.2173]	[.0142,.2059]	[.4634,.7448]	
	Number of participants	12	3	2	30	47
Hungary	Proportion	0.463	0.045	0.0285	0.4636	1
	(95%CI)	[.3207,.6115]	[.0134,.1407]	[.007,.1084]	[.3193,.6142]	
	Number of participants	27	3	2	29	61
Israel	Proportion	0.5549	0	0	0.4451	1
	(95%CI)	[.3274,.7614]			[.2386,.6726]	
	Number of participants	10	0	0	8	18
Italy	Proportion	0.5035	0.0123	0.0184	0.4658	1
	(95%CI)	[.3885,.6181]	[.003,.0484]	[.0059,.0564]	[.3529,.5824]	
	Number of participants	54	2	3	52	111
Latvia	Proportion	0.6853	0	0	0.3147	1
	(95%CI)	[.1638,.9603]			[.0397,.8362]	
	Number of participants	2	0	0	1	3
Lithuania	Proportion	1	0	0	0	1
	(95%CI)					
	Number of participants	4	0	0	0	4

Poland	Proportion (95%CI)	0.0161 [.0037,.0666]	0.0519 [.0094,.2395]	0	0.932 [.7688,.9826]	1
	Number of participants	2	2	0	30	34
Slovenia	Proportion (95%CI)	0.626 [.4954,.7405]	0.0088 [.0012,.0602]	0.0626 [.0229,.1601]	0.3026 [.1986,.4318]	1
	Number of participants	40	1	4	23	68
Spain	Proportion (95%CI)	0.21 [.1445,.2949]	0.0198 [.0057,.0657]	0.0155 [.0037,.0633]	0.7548 [.6671,.8254]	1
	Number of participants	29	3	2	92	126
Switzerland	Proportion (95%CI)	0.68 [.4844,.8278]	0.0218 [.003,.1415]	0.2025 [.0834,.4149]	0.0956 [.0352,.2349]	1
	Number of participants	22	1	5	4	32
Ukraine	Proportion (95%CI)	0.3173 [.1744,.5057]	0.0856 [.0327,.2056]	0.0125 [.0017,.0853]	0.5846 [.4078,.742]	1
	Number of participants	12	5	1	26	44
Total	Proportion (95%CI)	0.4202 [.3812,.4602]	0.0274 [.018,.0415]	0.043 [.0297,.0617]	0.5095 [.4692,.5496]	1
	Number of participants	339	25	33	398	795

Country	**CRP**

		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.0574 [.0205,.1504]	0.0294 [.0068,.1176]	0.0769 [.0327,.1702]	0.8363 [.721,.9099]	1
	Number of participants	4	2	6	51	63
Belgium	Proportion (95%CI)	0.0997 [.0129,.4836]	0.2674 [.0622,.6678]	0.1677 [.0232,.6312]	0.4652 [.1529,.8074]	1
	Number of participants	1	2	1	3	7
Croatia	Proportion (95%CI)	0	0	0.2877 [.0897,.6233]	0.7123 [.3767,.9103]	1
	Number of participants	0	0	3	6	9
Cyprus	Proportion (95%CI)	0.08 [.0113,.3989]	0.0391 [.0053,.2371]	0.3991 [.1921,.6499]	0.4817 [.2524,.7189]	1
	Number of participants	1	1	7	8	17
Czech Rep.	Proportion (95%CI)	0	0.0531 [.0067,.317]	0	0.9469 [.683,.9933]	1
	Number of participants	0	1	0	11	12
Finland	Proportion (95%CI)	0	0.3421 [.0612,.8056]	0.0614 [.0076,.3571]	0.5965 [.1908,.9026]	1

	Number of participants	0	1	1	8	10
France	Proportion (95%CI)	0.1891 [.1145,.296]	0.0476 [.0107,.1878]	0.0492 [.0182,.1257]	0.7142 [.5901,.8127]	1
	Number of participants	15	2	4	49	70
Germany	Proportion (95%CI)	0.2001 [.1162,.3224]	0.1109 [.0276,.3536]	0.0798 [.0328,.1815]	0.6093 [.4556,.744]	1
	Number of participants	13	3	5	38	59
Greece	Proportion (95%CI)	0.0381 [.0095,.1407]	0.2184 [.1203,.3633]	0.303 [.1869,.4512]	0.4405 [.3048,.5858]	1
	Number of participants	2	10	14	21	47
Hungary	Proportion (95%CI)	0.1006 [.0385,.2381]	0.0835 [.0326,.1977]	0.1052 [.0502,.2071]	0.7107 [.5667,.8219]	1
	Number of participants	5	5	8	43	61
Israel	Proportion (95%CI)	0.2088 [.079,.448]	0.1047 [.0258,.3405]	0.2376 [.092,.4894]	0.4489 [.2414,.6758]	1
	Number of participants	4	2	4	8	18
Italy	Proportion (95%CI)	0.0491 [.0241,.0973]	0.0307 [.0126,.0729]	0.0787 [.0407,.1469]	0.8415 [.7627,.8977]	1
	Number of participants	8	5	10	88	111
Latvia	Proportion	0	0.6853	0	0.3147	1

	(95%CI)		[.1638,.9603]		[.0397,.8362]	
	Number of participants	0	2	0	1	3
Lithuania	Proportion (95%CI)	0	0	0.8577 [.3519,.9853]	0.1423 [.0147,.6481]	1
	Number of participants	0	0	3	1	4
Poland	Proportion (95%CI)	0.1206 [.0288,.3879]	0.0603 [.0134,.2327]	0	0.8191 [.5754,.938]	1
	Number of participants	2	3	0	29	34
Slovenia	Proportion (95%CI)	0.0263 [.0083,.0796]	0.0509 [.0143,.1649]	0.5099 [.3814,.637]	0.413 [.2947,.5422]	1
	Number of participants	3	3	31	31	68
Spain	Proportion (95%CI)	0.1871 [.1235,.2732]	0.1182 [.0667,.2008]	0.0893 [.0502,.1538]	0.6055 [.5091,.6943]	1
	Number of participants	24	13	13	76	126
Switzerland	Proportion (95%CI)	0.2391 [.1202,.4196]	0	0.1343 [.0418,.3556]	0.6266 [.4336,.7862]	1
	Number of participants	9	0	3	20	32
Ukraine	Proportion (95%CI)	0.2265 [.1083,.4138]	0.0908 [.0353,.2144]	0.1461 [.0564,.3291]	0.5365 [.3641,.7006]	1
	Number of participants	9	5	5	25	44

Total	Proportion (95%CI)	0.1199 [.0974,.1467]	0.0819 [.0612,.1087]	0.1461 [.1213,.175]	0.6521 [.6135,.6889]	1
	Number of participants	100	60	118	517	795

Country		**Procalcitonin**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.6056 [.4654,.7303]	0.0086 [.0012,.0592]	0.0171 [.0042,.0673]	0.3687 [.2482,.5081]	1
	Number of participants	34	1	2	26	63
Belgium	Proportion (95%CI)	0.6962 [.2988,.9249]	0	0.1677 [.0232,.6312]	0.1361 [.0182,.5722]	1
	Number of participants	5	0	1	1	7
Croatia	Proportion (95%CI)	0.6773 [.3357,.8971]	0	0.0959 [.0129,.4624]	0.2268 [.0556,.5938]	1
	Number of participants	6	0	1	2	9
Cyprus	Proportion (95%CI)	0.4817 [.2524,.7189]	0	0.2366 [.0932,.4832]	0.2817 [.1087,.5578]	1
	Number of participants	8	0	5	4	17
Czech Rep.	Proportion (95%CI)	0.9469 [.683,.9933]	0	0.0531 [.0067,.317]	0	1

	Number of participants	11	0	1	0	12
Finland	Proportion (95%CI)	0.9035 [.5226,.9877]	0	0	0.0965 [.0123,.4774]	1
	Number of participants	9	0	0	1	10
France	Proportion (95%CI)	0.3352 [.2266,.4646]	0.0449 [.0096,.186]	0.0921 [.0377,.2081]	0.5278 [.3991,.6528]	1
	Number of participants	24	2	6	38	70
Germany	Proportion (95%CI)	0.5941 [.4554,.7193]	0.0321 [.0078,.1232]	0.0737 [.0302,.1688]	0.3001 [.1935,.4339]	1
	Number of participants	33	2	5	19	59
Greece	Proportion (95%CI)	0.4147 [.2826,.5604]	0.138 [.0622,.2786]	0.1761 [.0892,.318]	0.2712 [.1624,.4168]	1
	Number of participants	20	6	8	13	47
Hungary	Proportion (95%CI)	0.3303 [.2103,.4773]	0.0285 [.007,.1084]	0.1207 [.0574,.2363]	0.5205 [.3734,.6641]	1
	Number of participants	22	2	8	29	61
Israel	Proportion (95%CI)	0.7768 [.5305,.9147]	0.0458 [.0063,.266]	0.0639 [.009,.3404]	0.1135 [.0282,.3611]	1
	Number of participants	14	1	1	2	18
Italy	Proportion	0.5211	0.0184	0.0603	0.4002	1

	(95%CI)	[.4052,.6347]	[.0059,.0564]	[.0275,.1272]	[.2915,.5197]	
	Number of participants	57	3	7	44	111
Latvia	Proportion (95%CI)	0.6294 [.1328,.9496]	0	0.3706 [.0504,.8672]	0	1
	Number of participants	2	0	1	0	3
Lithuania	Proportion (95%CI)	1	0	0	0	1
	Number of participants	4	0	0	0	4
Poland	Proportion (95%CI)	0.1444 [.0428,.389]	0.0603 [.0134,.2327]	0.0084 [.0011,.0603]	0.7869 [.5553,.9161]	1
	Number of participants	5	3	1	25	34
Slovenia	Proportion (95%CI)	0.6597 [.5237,.7736]	0.0218 [.0053,.086]	0.096 [.0348,.2381]	0.2225 [.1331,.3479]	1
	Number of participants	46	2	4	16	68
Spain	Proportion (95%CI)	0.2625 [.1873,.3549]	0.1165 [.0649,.2005]	0.049 [.0221,.105]	0.5719 [.4754,.6633]	1
	Number of participants	34	12	7	73	126
Switzerland	Proportion (95%CI)	0.9001 [.7566,.9632]	0	0	0.0999 [.0368,.2434]	1
	Number of participants	28	0	0	4	32

Ukraine	Proportion (95%CI)	0.6221 [.4458,.7711]	0.0303 [.0072,.1179]	0.1211 [.0414,.3055]	0.2265 [.1157,.3958]	1
	Number of participants	27	2	4	11	44
Total	Proportion (95%CI)	0.4939 [.4537,.5342]	0.045 [.0315,.064]	0.0777 [.0595,.1008]	0.3834 [.3449,.4234]	1
	Number of participants	389	36	62	308	795

Country		**Full blood count**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.0749 [.0298,.1759]	0.0499 [.0176,.133]	0.1142 [.0567,.2164]	0.7611 [.6353,.8535]	1
	Number of participants	5	4	9	45	63
Belgium	Proportion (95%CI)	0.0997 [.0129,.4836]	0.2674 [.0622,.6678]	0.0997 [.0129,.4836]	0.5332 [.1966,.8421]	1
	Number of participants	1	2	1	3	7
Croatia	Proportion (95%CI)	0	0	0.5145 [.2126,.8061]	0.4855 [.1939,.7874]	1
	Number of participants	0	0	5	4	9
Cyprus	Proportion (95%CI)	0.1626 [.0419,.4628]	0.0391 [.0053,.2371]	0.5574 [.3115,.7781]	0.2409 [.088,.5106]	1

	Number of participants	2	1	10	4	17
Czech Re	Proportion (95%CI)	0.5778 [.2547,.8456]	0	0.3691 [.1314,.6935]	0.0531 [.0067,.317]	1
	Number of participants	5	0	6	1	12
Finland	Proportion (95%CI)	0.2193 [.058,.5619]	0.3421 [.0612,.8056]	0.0614 [.0076,.3571]	0.3772 [.1215,.7262]	1
	Number of participants	3	1	1	5	10
France	Proportion (95%CI)	0.3946 [.2805,.5214]	0.011 [.0015,.0746]	0.2378 [.1436,.3673]	0.3566 [.2405,.4923]	1
	Number of participants	30	1	16	23	70
Germany	Proportion (95%CI)	0.2385 [.1447,.367]	0.0979 [.0205,.3605]	0.1727 [.0955,.2921]	0.4909 [.3529,.6304]	1
	Number of participants	15	2	11	31	59
Greece	Proportion (95%CI)	0.0571 [.0184,.1637]	0.2294 [.1266,.3794]	0.3576 [.2335,.5044]	0.3559 [.2316,.5032]	1
	Number of participants	3	10	17	17	47
Hungary	Proportion (95%CI)	0.1541 [.0727,.2975]	0.089 [.0356,.2054]	0.1906 [.1103,.3091]	0.5662 [.4187,.7029]	1
	Number of participants	8	5	15	33	61
Israel	Proportion	0.1592	0.1687	0.2376	0.4345	1

	(95%CI)	[.0512,.3993]	[.0547,.4155]	[.092,.4894]	[.2309,.6628]	
	Number of participants	3	3	4	8	18
Italy	Proportion (95%CI)	0.206 [.1251,.3202]	0.0616 [.0308,.1193]	0.1759 [.1138,.2619]	0.5565 [.4416,.6657]	1
	Number of participants	22	9	23	57	111
Latvia	Proportion (95%CI)	0	0.3147 [.0397,.8362]	0.6853 [.1638,.9603]	0	1
	Number of participants	0	1	2	0	3
Lithuania	Proportion (95%CI)	0	0	0.8577 [.3519,.9853]	0.1423 [.0147,.6481]	1
	Number of participants	0	0	3	1	4
Poland	Proportion (95%CI)	0.0154 [.0036,.0637]	0.0687 [.0177,.2315]	0.136 [.0377,.3872]	0.78 [.5503,.9112]	1
	Number of participants	2	4	4	24	34
Slovenia	Proportion (95%CI)	0.0175 [.0043,.0683]	0.0717 [.0291,.166]	0.552 [.4232,.6742]	0.3588 [.2484,.4865]	1
	Number of participants	2	5	33	28	68
Spain	Proportion (95%CI)	0.3529 [.2671,.4494]	0.0882 [.0458,.1633]	0.2625 [.1873,.3549]	0.2963 [.2182,.3885]	1
	Number of participants	44	10	34	38	126

Switzerland	Proportion (95%CI)	0.2651 [.1389,.4466]	0	0.1821 [.0726,.3878]	0.5527 [.367,.7248]	1
	Number of participants	10	0	5	17	32
Ukraine	Proportion (95%CI)	0.2067 [.0926,.3996]	0.0783 [.0275,.2033]	0.3904 [.244,.5596]	0.3246 [.1796,.5133]	1
	Number of participants	7	4	21	12	44
Total	Proportion (95%CI)	0.2032 [.173,.2371]	0.0805 [.0605,.1065]	0.2623 [.23,.2974]	0.454 [.4139,.4946]	1
	Number of participants	162	62	220	351	795

Country		**Blood gas analysis (with or without lactate)**		
		I would not use the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.7965 [.6277,.9009]	0.2035 [.0991,.3723]	1
	Number of participants	52	11	63
Belgium	Proportion (95%CI)	0.5965 [.2371,.8755]	0.4035 [.1245,.7629]	1

	Number of participants	4	3	7
Croatia	Proportion (95%CI)	0.6773 [.3357,.8971]	0.3227 [.1029,.6643]	1
	Number of participants	6	3	9
Cyprus	Proportion (95%CI)	0.9609 [.7629,.9947]	0.0391 [.0053,.2371]	1
	Number of participants	16	1	17
Czech Re	Proportion (95%CI)	0.8155 [.5094,.9495]	0.1845 [.0505,.4906]	1
	Number of participants	9	3	12
Finland	Proportion (95%CI)	0.9386 [.6429,.9924]	0.0614 [.0076,.3571]	1
	Number of participants	9	1	10
France	Proportion (95%CI)	0.9058 [.7889,.9611]	0.0942 [.0389,.2111]	1
	Number of participants	64	6	70
Germany	Proportion (95%CI)	0.8411 [.7232,.9147]	0.1589 [.0853,.2768]	1
	Number of participants	49	10	59
Greece	Proportion	0.8472	0.1528	1

	(95%CI)	[.7082,.9269]	[.0731,.2918]	
	Number of participants	40	7	47
Hungary	Proportion	0.6304	0.3696	1
	(95%CI)	[.4698,.7666]	[.2334,.5302]	
	Number of participants	39	22	61
Israel	Proportion	0.8721	0.1279	1
	(95%CI)	[.6095,.9675]	[.0325,.3905]	
	Number of participants	16	2	18
Italy	Proportion	0.8322	0.1678	1
	(95%CI)	[.714,.9079]	[.0921,.286]	
	Number of participants	96	15	111
Latvia	Proportion	0.6853	0.3147	1
	(95%CI)	[.1638,.9603]	[.0397,.8362]	
	Number of participants	2	1	3
Lithuania	Proportion	1	0	1
	(95%CI)			
	Number of participants	4	0	4
Poland	Proportion	0.3699	0.6301	1
	(95%CI)	[.18,.6109]	[.3891,.82]	
	Number of participants	16	18	34

Slovenia	Proportion (95%CI)	0.9151 [.7835,.9698]	0.0849 [.0302,.2165]	1
	Number of participants	64	4	68
Spain	Proportion (95%CI)	0.8693 [.7842,.924]	0.1307 [.076,.2158]	1
	Number of participants	112	14	126
Switzerland	Proportion (95%CI)	0.91 [.7378,.9732]	0.09 [.0268,.2622]	1
	Number of participants	29	3	32
Ukraine	Proportion (95%CI)	0.778 [.6053,.889]	0.222 [.111,.3947]	1
	Number of participants	33	10	43
Total	Proportion (95%CI)	0.8162 [.7801,.8475]	0.1838 [.1525,.2199]	1
	Number of participants	660	134	794

Country		**Lactate**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion	0.8981	0.0277	0.0468	0.0274	1

	(95%CI)	[.7967,.952]	[.0062,.1149]	[.0142,.1438]	[.0086,.0837]	
	Number of participants	55	2	3	3	63
Belgium	Proportion (95%CI)	0.8323 [.3688,.9768]	0	0.1677 [.0232,.6312]	0	1
	Number of participants	6	0	1	0	7
Croatia	Proportion (95%CI)	0.8082 [.4621,.9539]	0	0.0959 [.0129,.4624]	0.0959 [.0129,.4624]	1
	Number of participants	7	0	1	1	9
Cyprus	Proportion (95%CI)	0.9609 [.7629,.9947]	0	0.0391 [.0053,.2371]	0	1
	Number of participants	16	0	1	0	17
Czech Re	Proportion (95%CI)	0.9469 [.683,.9933]	0.0531 [.0067,.317]	0	0	1
	Number of participants	11	1	0	0	12
Finland	Proportion (95%CI)	1	0	0	0	1
	Number of participants	10	0	0	0	10
France	Proportion (95%CI)	0.9416 [.8132,.9835]	0	0.0474 [.0106,.1876]	0.011 [.0015,.0746]	1
	Number of participants	67	0	2	1	70

Germany	Proportion (95%CI)	0.8881 [.6464,.9718]	0.0331 [.0081,.1257]	0.0788 [.0117,.3828]	0	1
	Number of participants	56	2	1	0	59
Greece	Proportion (95%CI)	0.8663 [.7281,.94]	0.0343 [.0049,.2056]	0.0614 [.0197,.1752]	0.0381 [.0095,.1407]	1
	Number of participants	41	1	3	2	47
Hungary	Proportion (95%CI)	0.865 [.7477,.9327]	0	0.0725 [.0266,.1831]	0.0625 [.0238,.1537]	1
	Number of participants	52	0	4	5	61
Israel	Proportion (95%CI)	0.9542 [.734,.9937]	0	0.0458 [.0063,.266]	0	1
	Number of participants	17	0	1	0	18
Italy	Proportion (95%CI)	0.8849 [.8068,.934]	0.0123 [.003,.0484]	0.0362 [.0143,.0884]	0.0667 [.0307,.1389]	1
	Number of participants	97	2	5	7	111
Latvia	Proportion (95%CI)	1	0	0	0	1
	Number of participants	3	0	0	0	3
Lithuania	Proportion (95%CI)	1	0	0	0	1
	Number of participants	4	0	0	0	4

Poland	Proportion (95%CI)	0.8374 [.6037,.9457]	0.0519 [.0094,.2395]	0.0771 [.0109,.388]	0.0336 [.0114,.0948]	1
	Number of participants	27	2	1	4	34
Slovenia	Proportion (95%CI)	0.891 [.7721,.9517]	0.0131 [.0018,.0876]	0.0829 [.0309,.2044]	0.0131 [.0018,.0876]	1
	Number of participants	62	1	4	1	68
Spain	Proportion (95%CI)	0.9319 [.8705,.9654]	0.01 [.0014,.0675]	0.0055 [7.7e-04,.0386]	0.0526 [.0243,.1099]	1
	Number of participants	117	1	1	7	126
Switzerland	Proportion (95%CI)	0.884 [.7138,.9588]	0	0.0218 [.003,.1415]	0.0942 [.0286,.2689]	1
	Number of participants	28	0	1	3	32
Ukraine	Proportion (95%CI)	0.8413 [.6624,.9348]	0	0	0.1587 [.0652,.3376]	1
	Number of participants	38	0	0	6	44
Total	Proportion (95%CI)	0.8973 [.8696,.9196]	0.0141 [.0077,.0259]	0.0448 [.0291,.0683]	0.0439 [.0311,.0615]	1
	Number of participants	714	12	29	40	795

Hospitals

Country		Urine dipstick				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion	0.108	0.8116	0.0152	0.0651	1
	(95%CI)	[.054,.2044]	[.6859,.8948]	[.0021,.1011]	[.0193,.1976]	
	Number of participants	11	60	1	3	75
Belgium	Proportion	0.1071	0.4579	0.2574	0.1777	1
	(95%CI)	[.0467,.227]	[.3005,.6241]	[.1448,.415]	[.0918,.316]	
	Number of participants	6	22	12	11	51
Bulgaria	Proportion	0.44	0.12	0	0.44	1
	(95%CI)	[.0975,.8511]	[.0143,.5616]		[.0975,.8511]	
	Number of participants	2	1	0	2	5
Croatia	Proportion	0.1307	0.3322	0.1307	0.4064	1
	(95%CI)	[.0409,.3468]	[.1832,.5244]	[.0517,.2932]	[.2302,.6104]	
	Number of participants	4	11	5	9	29
Cyprus	Proportion	0	0.5437	0	0.4563	1
	(95%CI)		[.2253,.83]		[.17,.7747]	
	Number of participants	0	5	0	7	12
Czech Re	Proportion	0	0	1	0	1
	(95%CI)					

	Number of participants	0	0	1	0	1
Denmark	Proportion (95%CI)	0	1	0	0	1
	Number of participants	0	5	0	0	5
Finland	Proportion (95%CI)	0.2321 [.0992,.4534]	0.4852 [.2927,.6822]	0.0549 [.0077,.3018]	0.2278 [.0972,.4472]	1
	Number of participants	5	13	1	5	24
France	Proportion (95%CI)	0.0208 [.0028,.1369]	0.9792 [.8631,.9972]	0	0	1
	Number of participants	1	30	0	0	31
Germany	Proportion (95%CI)	0.1043 [.023,.3653]	0.7791 [.5359,.9151]	0	0.1166 [.03,.3601]	1
	Number of participants	3	43	0	5	51
Greece	Proportion (95%CI)	0.0574 [.0179,.1689]	0.4147 [.2755,.569]	0.2137 [.1202,.3509]	0.3142 [.1975,.4603]	1
	Number of participants	4	24	14	22	64
Hungary	Proportion (95%CI)	0.1864 [.046,.5214]	0.7119 [.4169,.8951]	0.0508 [.0069,.2931]	0.0508 [.0069,.2931]	1
	Number of participants	2	10	1	1	14

Ireland	Proportion (95%CI)	0	1	0	0	1
	Number of participants	0	3	0	0	3
Israel	Proportion (95%CI)	0.8421 [.2492,.9885]	0.1579 [.0115,.7508]	0	0	1
	Number of participants	1	1	0	0	2
Italy	Proportion (95%CI)	0.2617 [.0895,.5612]	0.7383 [.4388,.9105]	0	0	1
	Number of participants	7	20	0	0	27
Latvia	Proportion (95%CI)	0.0444 [.0055,.2798]	0.6222 [.2471,.8921]	0.2333 [.035,.7184]	0.1 [.0212,.3628]	1
	Number of participants	1	5	1	2	9
Lithuania	Proportion (95%CI)	0	0.3646 [.1305,.6869]	0.1562 [.0423,.4368]	0.4792 [.1616,.8146]	1
	Number of participants	0	7	3	2	12
Malta	Proportion (95%CI)	0.1671 [.0793,.3185]	0.7062 [.544,.8289]	0.0728 [.0235,.2039]	0.0539 [.0127,.2013]	1
	Number of participants	7	27	3	2	39
Netherlands	Proportion (95%CI)	0.0702 [.0212,.2083]	0.4048 [.2722,.5529]	0.2828 [.1666,.4375]	0.2421 [.1395,.3864]	1

	Number of participants	3	22	12	13	50
Norway	Proportion (95%CI)	0.1511 [.0789,.27]	0.7127 [.5701,.8227]	0.0448 [.0104,.1723]	0.0914 [.0331,.2285]	1
	Number of participants	9	38	2	4	53
Poland	Proportion (95%CI)	0.458 [.3264,.5957]	0.2465 [.1433,.3901]	0.1667 [.0907,.2861]	0.1289 [.0578,.263]	1
	Number of participants	39	17	20	8	84
Portugal	Proportion (95%CI)	0.125 [.0545,.2615]	0.5848 [.3975,.7505]	0.2321 [.0995,.4528]	0.058 [.0175,.1757]	1
	Number of participants	8	29	7	4	48
Romania	Proportion (95%CI)	0.1071 [.0141,.5011]	0.7857 [.4143,.95]	0	0.1071 [.0141,.5011]	1
	Number of participants	1	5	0	1	7
Slovenia	Proportion (95%CI)	0.1522 [.0668,.3105]	0.3602 [.198,.5622]	0.2547 [.1171,.468]	0.2329 [.101,.4506]	1
	Number of participants	6	12	8	7	33
Spain	Proportion (95%CI)	0.0963 [.0474,.186]	0.8182 [.7146,.89]	0.0393 [.0122,.1193]	0.0461 [.0188,.1089]	1
	Number of participants	9	53	3	5	70
Sweden	Proportion	0.04	0.96	0	0	1

	(95%CI)	[.0049,.2591]	[.7409,.9951]			
	Number of participants	1	11	0	0	12
Switzerland	Proportion (95%CI)	0.1512 [.0527,.3633]	0.7512 [.52,.8938]	0.0976 [.0238,.3237]	0	1
	Number of participants	4	16	2	0	22
Ukraine	Proportion (95%CI)	0.1213 [.0465,.2809]	0.6255 [.4527,.7713]	0.0983 [.035,.2471]	0.1548 [.0626,.3342]	1
	Number of participants	7	33	7	6	53
United K	Proportion (95%CI)	0.0764 [.0321,.1711]	0.8701 [.7697,.9306]	0.0535 [.0211,.1291]	0	1
	Number of participants	6	65	5	0	76
Total	Proportion (95%CI)	0.1421 [.1178,.1703]	0.6233 [.586,.6593]	0.1086 [.0876,.134]	0.126 [.1029,.1534]	1
	Number of participants	147	588	108	119	962

Country		**RSV**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.5069 [.3695,.6433]	0.0803 [.0284,.2072]	0.1025 [.0439,.2211]	0.3102 [.1996,.448]	1

	Number of participants	37	5	8	25 75	
Belgium	Proportion (95%CI)	0.5057 [.3463,.6639]	0.041 [.0101,.1515]	0.0661 [.0186,.2089]	0.3872 [.2496,.5456]	1
	Number of participants	23	2	3	23	51
Bulgaria	Proportion (95%CI)	0.12 [.0143,.5616]	0	0.12 [.0143,.5616]	0.76 [.3343,.9523]	1
	Number of participants	1	0	1	3	5
Croatia	Proportion (95%CI)	0.4594 [.2773,.6529]	0.0106 [.0014,.0736]	0.1131 [.0358,.3047]	0.417 [.2435,.6138]	1
	Number of participants	12	1	3	13	29
Cyprus	Proportion (95%CI)	0.3689 [.0886,.7785]	0.1262 [.028,.4205]	0.3883 [.1411,.7105]	0.1165 [.0257,.397]	1
	Number of participants	2	2	6	2	12
Czech Rep.	Proportion (95%CI)	1	0	0	0	1
	Number of participants	1	0	0	0	1
Denmark	Proportion (95%CI)	0.2 [.0264,.6975]	0	0	0.8 [.3025,.9736]	1
	Number of participants	1	0	0	4	5
Finland	Proportion	0.4346	0.1055	0	0.4599	1

	(95%CI)	[.2499,.6394]	[.0268,.3356]		[.2721,.6598]	
	Number of participants	10	2	0	12	24
France	Proportion	0.5117	0	0.0779	0.4104	1
	(95%CI)	[.307,.7125]		[.0168,.2943]	[.226,.6239]	
	Number of participants	17	0	2	12	31
Germany	Proportion	0.319	0.0184	0.2945	0.3681	1
	(95%CI)	[.1743,.5097]	[.0025,.1222]	[.1303,.5376]	[.2104,.5601]	
	Number of participants	22	1	8	20	51
Greece	Proportion	0.2823	0.0159	0.0447	0.6571	1
	(95%CI)	[.176,.42]	[.0022,.1057]	[.0151,.1244]	[.5162,.7749]	
	Number of participants	23	1	4	36	64
Hungary	Proportion	0.2966	0.2373	0.1695	0.2966	1
	(95%CI)	[.1204,.565]	[.0644,.5843]	[.0392,.5052]	[.1202,.5656]	
	Number of participants	5	2	2	5	14
Ireland	Proportion	0	0	0	1	1
	(95%CI)					
	Number of participants	0	0	0	3	3
Israel	Proportion	0.8421	0	0	0.1579	1
	(95%CI)	[.2492,.9885]			[.0115,.7508]	
	Number of participants	1	0	0	1	2

Italy	Proportion (95%CI)	0.5 [.2481,.7519]	0	0.0973 [.0182,.3854]	0.4027 [.1806,.6734]	1
	Number of participants	14	0	2	11	27
Latvia	Proportion (95%CI)	0.2 [.039,.6062]	0	0.2333 [.035,.7184]	0.5667 [.2088,.8663]	1
	Number of participants	2	0	1	6	9
Lithuania	Proportion (95%CI)	0.8958 [.6302,.9775]	0	0	0.1042 [.0225,.3698]	1
	Number of participants	10	0	0	2	12
Malta	Proportion (95%CI)	0.2049 [.1004,.373]	0.0728 [.0235,.2039]	0.1509 [.0633,.3187]	0.5714 [.4075,.7211]	1
	Number of participants	7	3	5	24	39
Netherlands	Proportion (95%CI)	0.7246 [.5792,.8341]	0.0388 [.0121,.1178]	0.0222 [.0054,.0859]	0.2144 [.1163,.3615]	1
	Number of participants	35	3	2	10	50
Norway	Proportion (95%CI)	0.403 [.2763,.5441]	0.056 [.0179,.1619]	0.1847 [.0938,.3314]	0.3563 [.2371,.4965]	1
	Number of participants	22	3	8	20	53
Poland	Proportion (95%CI)	0.1036 [.0431,.2291]	0.0084 [.0021,.0338]	0.0112 [.0026,.0464]	0.8768 [.7567,.9421]	1

	Number of participants	8	2	2	72	84
Portugal	Proportion (95%CI)	0.7589 [.5983,.8694]	0	0.0491 [.0126,.1733]	0.192 [.0969,.3447]	1
	Number of participants	34	0	3	11	48
Romania	Proportion (95%CI)	0.3214 [.0827,.7134]	0	0	0.6786 [.2866,.9173]	1
	Number of participants	2	0	0	5	7
Slovenia	Proportion (95%CI)	0.6522 [.4683,.7997]	0.0497 [.012,.1836]	0	0.2981 [.1649,.4775]	1
	Number of participants	19	2	0	12	33
Spain	Proportion (95%CI)	0.2877 [.1877,.4138]	0.0163 [.004,.0637]	0.0638 [.0248,.1545]	0.6323 [.5044,.7439]	1
	Number of participants	22	2	5	41	70
Sweden	Proportion (95%CI)	0.59 [.2101,.8862]	0	0.33 [.0673,.7708]	0.08 [.0168,.307]	1
	Number of participants	8	0	2	2	12
Switzerland	Proportion (95%CI)	0.7415 [.5201,.8836]	0	0	0.2585 [.1164,.4799]	1
	Number of participants	14	0	0	8	22
Ukraine	Proportion	0.2029	0.0418	0.0167	0.7385	1

	(95%CI)	[.1019,.3637]	[.0167,.1009]	[.0041,.0663]	[.5825,.8511]	
	Number of participants	11	5	2	35	53
UK	Proportion (95%CI)	0.2701 [.1751,.392]	0.1185 [.0595,.2222]	0.1758 [.0993,.2921]	0.4357 [.3212,.5574]	1
	Number of participants	20	9	12	35	76
Total	Proportion (95%CI)	0.4001 [.3632,.4382]	0.0415 [.03,.0571]	0.0931 [.0719,.1198]	0.4653 [.4277,.5033]	1
	Number of participants	383	45	81	453	962

Country		**Influenza**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.4474 [.3168,.5856]	0.0457 [.015,.1312]	0.1787 [.0846,.3386]	0.3283 [.2115,.471]	1
	Number of participants	36	4	11	24	75
Belgium	Proportion (95%CI)	0.4943 [.3353,.6545]	0.041 [.0101,.1515]	0.0661 [.0186,.2089]	0.3986 [.2585,.5576]	1
	Number of participants	23	2	3	23	51

Bulgaria	Proportion (95%CI)	0.12 [.0143,.5616]	0	0.12 [.0143,.5616]	0.76 [.3343,.9523]	1
	Number of participants	1	0	1	3	5
Croatia	Proportion (95%CI)	0.53 [.3378,.7137]	0.0106 [.0014,.0736]	0.0636 [.0157,.2242]	0.3958 [.2234,.5986]	1
	Number of participants	15	1	2	11	29
Cyprus	Proportion (95%CI)	0.3689 [.0886,.7785]	0.1262 [.028,.4205]	0.3204 [.1108,.6408]	0.1845 [.0515,.4852]	1
	Number of participants	2	2	5	3	12
Czech Rep.	Proportion (95%CI)	1	0	0	0	1
	Number of participants	1	0	0	0	1
Denmark	Proportion (95%CI)	0.2 [.0264,.6975]	0	0	0.8 [.3025,.9736]	1
	Number of participants	1	0	0	4	5

Finland	Proportion (95%CI)	0.308 [.1526,.5239]	0.1055 [.0268,.3356]	0.0549 [.0077,.3018]	0.5316 [.3307,.7229]	1
	Number of participants	7	2	1	14	24
France	Proportion (95%CI)	0.5117 [.307,.7125]	0	0.0571 [.008,.3119]	0.4312 [.2426,.6421]	1
	Number of participants	17	0	1	13	31
Germany	Proportion (95%CI)	0.4785 [.2928,.6704]	0.0368 [.0089,.1398]	0.1227 [.0331,.3638]	0.362 [.1962,.5686]	1
	Number of participants	28	2	4	17	51
Greece	Proportion (95%CI)	0.1834 [.1024,.3067]	0.075 [.0236,.2137]	0.0064 [8.8e-04,.0447]	0.7352 [.5949,.84]	1
	Number of participants	17	3	1	43	64
Hungary	Proportion (95%CI)	0.2288 [.0832,.4925]	0.2373 [.0644,.5843]	0.1695 [.0392,.5052]	0.3644 [.1605,.6322]	1
	Number of participants	4	2	2	6	14

Ireland	Proportion (95%CI)	0	0	0	1	1
	Number of participants	0	0	0	3	3
Israel	Proportion (95%CI)	0.8421 [.2492,.9885]	0	0	0.1579 [.0115,.7508]	1
	Number of participants	1	0	0	1	2
Italy	Proportion (95%CI)	0.5034 [.2507,.7543]	0	0.0805 [.0112,.4041]	0.4161 [.1902,.6837]	1
	Number of participants	14	0	1	12	27
Latvia	Proportion (95%CI)	0	0	0.2333 [.035,.7184]	0.7667 [.2816,.965]	1
	Number of participants	0	0	1	8	9
Lithuania	Proportion (95%CI)	0.7396 [.4325,.9137]	0.0521 [.0066,.3136]	0.1042 [.0225,.3698]	0.1042 [.0225,.3698]	1
	Number of participants	7	1	2	2	12

Malta	Proportion (95%CI)	0.2237 [.1147,.3906]	0.0728 [.0235,.2039]	0.1509 [.0633,.3187]	0.5526 [.3906,.7041]	1
	Number of participants	8	3	5	23	39
Netherlands	Proportion (95%CI)	0.6691 [.5196,.7909]	0.0388 [.0121,.1178]	0.0222 [.0054,.0859]	0.2699 [.1574,.4223]	1
	Number of participants	33	3	2	12	50
Norway	Proportion (95%CI)	0.4683 [.3341,.6073]	0.0354 [.0087,.1336]	0.1903 [.1001,.3318]	0.306 [.1948,.4455]	1
	Number of participants	25	2	9	17	53
Poland	Proportion (95%CI)	0.0084 [.0021,.0338]	0.0084 [.0021,.0338]	0.0182 [.0056,.0577]	0.965 [.9241,.9842]	1
	Number of participants	2	2	3	77	84
Portugal	Proportion (95%CI)	0.75 [.5878,.8632]	0	0.0402 [.0081,.1764]	0.2098 [.1095,.3645]	1

	Number of participants	34	0	2	12	48
Romania	Proportion (95%CI)	0.3214 [.0827,.7134]	0	0	0.6786 [.2866,.9173]	1
	Number of participants	2	0	0	5	7
Slovenia	Proportion (95%CI)	0.4224 [.2417,.6264]	0.0217 [.003,.1416]	0.0217 [.003,.1416]	0.5342 [.3387,.7197]	1
	Number of participants	12	1	1	19	33
Spain	Proportion (95%CI)	0.1696 [.0964,.2812]	0.0081 [.0011,.0561]	0.1153 [.0556,.2239]	0.7069 [.5821,.8069]	1
	Number of participants	14	1	8	47	70
Sweden	Proportion (95%CI)	0.63 [.2222,.9103]	0	0.33 [.0673,.7708]	0.04 [.0049,.2591]	1
	Number of participants	9	0	2	1	12
Switzerland	Proportion (95%CI)	0.6049 [.3708,.7991]	0	0	0.3951 [.2009,.6292]	1

	Number of participants	11	0	0	11	22
Ukraine	Proportion (95%CI)	0.1569 [.0735,.3041]	0.0502 [.0193,.1244]	0.0251 [.0078,.0776]	0.7678 [.6225,.8689]	1
	Number of participants	10	5	3	35	53
UK	Proportion (95%CI)	0.2892 [.192,.4105]	0.1108 [.0536,.2152]	0.1261 [.0642,.2329]	0.4739 [.3559,.5948]	1
	Number of participants	22	8	9	37	76
Total	Proportion (95%CI)	0.3642 [.3282,.4019]	0.0414 [.0299,.057]	0.0875 [.0676,.1126]	0.5069 [.4688,.5449]	1
	Number of participants	356	44	79	483	962

Country		**CRP**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.1219 [.0618,.2262]	0.0762 [.0322,.1696]	0.205 [.1057,.36]	0.597 [.4543,.7249]	1

	Number of participants	11	7	14	43	75
Belgium	Proportion (95%CI)	0.1913 [.1031,.3275]	0.0501 [.0151,.154]	0.2528 [.1175,.4623]	0.5057 [.3456,.6647]	1
	Number of participants	13	3	8	27	51
Bulgaria	Proportion (95%CI)	0	0	0.56 [.1489,.9025]	0.44 [.0975,.8511]	1
	Number of participants	0	0	3	2	5
Croatia	Proportion (95%CI)	0.1696 [.063,.3831]	0.1095 [.0314,.3184]	0.583 [.3862,.7565]	0.1378 [.0575,.2952]	1
	Number of participants	4	3	16	6	29
Cyprus	Proportion (95%CI)	0	0.0583 [.0074,.3376]	0.3883 [.1411,.7105]	0.5534 [.2344,.8338]	1
	Number of participants	0	1	6	5	12
Czech Rep.	Proportion (95%CI)	0	0	1	0	1
	Number of participants	0	0	1	0	1
Denmark	Proportion (95%CI)	0	0.2 [.0264,.6975]	0.2857 [.0614,.7098]	0.5143 [.1454,.8682]	1
	Number of participants	0	1	2	2	5
Finland	Proportion	0	0.0506	0.3882	0.5612	1

	(95%CI)		[.0071,.2843]	[.2129,.5981]	[.3566,.7469]	
	Number of participants	0	1	9	14	24
France	Proportion	0.3143	0	0.1429	0.5429	1
	(95%CI)	[.1682,.5095]		[.0459,.3659]	[.3376,.7345]	
	Number of participants	15	0	4	12	31
Germany	Proportion	0.2086	0.0491	0.2577	0.4847	1
	(95%CI)	[.0902,.412]	[.0157,.143]	[.1124,.4874]	[.2978,.6759]	
	Number of participants	10	4	10	27	51
Greece	Proportion	0.1021	0.2201	0.3142	0.3636	1
	(95%CI)	[.0507,.1949]	[.1227,.3629]	[.1975,.4603]	[.2286,.5243]	
	Number of participants	10	13	22	19	64
Hungary	Proportion	0	0.1186	0.4831	0.3983	1
	(95%CI)		[.0171,.51]	[.2339,.7409]	[.1833,.6612]	
	Number of participants	0	1	6	7	14
Ireland	Proportion	0.4667	0	0	0.5333	1
	(95%CI)	[.0695,.9111]			[.0889,.9305]	
	Number of participants	1	0	0	2	3
Israel	Proportion	0	0	0.1579	0.8421	1
	(95%CI)			[.0115,.7508]	[.2492,.9885]	
	Number of participants	0	0	1	1	2

Italy	Proportion (95%CI)	0.1644 [.0329,.5326]	0.1074 [.0231,.3793]	0.2919 [.1098,.5795]	0.4362 [.2041,.7001]	1
	Number of participants	3	3	9	12	27
Latvia	Proportion (95%CI)	0.2889 [.0603,.7202]	0	0.1 [.0212,.3628]	0.6111 [.2408,.8861]	1
	Number of participants	2	0	2	5	9
Lithuania	Proportion (95%CI)	0.5313 [.2079,.8303]	0	0.2604 [.0863,.5675]	0.2083 [.064,.5033]	1
	Number of participants	3	0	5	4	12
Malta	Proportion (95%CI)	0.1752 [.0844,.3286]	0.2022 [.1026,.3596]	0.1402 [.0582,.3007]	0.4825 [.3279,.6405]	1
	Number of participants	7	8	5	19	39
Netherlands	Proportion (95%CI)	0.1294 [.0569,.268]	0.0425 [.0103,.1595]	0.2847 [.1702,.4357]	0.5434 [.3958,.6838]	1
	Number of participants	6	2	14	28	50
Norway	Proportion (95%CI)	0	0.0802 [.0331,.1817]	0.4907 [.3544,.6283]	0.4291 [.299,.5698]	1
	Number of participants	0	5	25	23	53
Poland	Proportion (95%CI)	0.0042 [5.8e-04,.0297]	0.1303 [.059,.2634]	0.049 [.0153,.1457]	0.8165 [.6824,.9021]	1

	Number of participants	1	9	5	69	84
Portugal	Proportion (95%CI)	0.3259 [.1902,.4988]	0.058 [.0163,.1862]	0.2589 [.1405,.4274]	0.3571 [.1904,.5676]	1
	Number of participants	18	3	14	13	48
Romania	Proportion (95%CI)	0.1786 [.0253,.6455]	0	0.25 [.0595,.6372]	0.5714 [.2245,.8599]	1
	Number of participants	1	0	2	4	7
Slovenia	Proportion (95%CI)	0	0.0745 [.0234,.2134]	0.3758 [.2108,.5756]	0.5497 [.3561,.7293]	1
	Number of participants	0	3	13	17	33
Spain	Proportion (95%CI)	0.4396 [.3192,.5676]	0.0163 [.004,.0637]	0.2374 [.1404,.3726]	0.3066 [.2,.439]	1
	Number of participants	35	2	13	20	70
Sweden	Proportion (95%CI)	0.12 [.0314,.3649]	0	0	0.88 [.6351,.9686]	1
	Number of participants	3	0	0	9	12
Switzerland	Proportion (95%CI)	0.2537 [.1086,.4868]	0.0439 [.006,.2591]	0.239 [.0773,.5407]	0.4634 [.2402,.7023]	1
	Number of participants	6	1	4	11	22
Ukraine	Proportion	0.228	0.0669	0.1213	0.5837	1

	(95%CI)	[.1171,.3969]	[.0297,.144]	[.0458,.2844]	[.4179,.7325]	
	Number of participants	13	7	6	27	53
UK	Proportion	0.065	0.149	0.321	0.465	1
	(95%CI)	[.0273,.147]	[.0774,.2677]	[.22,.4421]	[.3476,.5863]	
	Number of participants	6	9	26	35	76
Total	Proportion	0.1583	0.0852	0.2585	0.498	1
	(95%CI)	[.1334,.1869]	[.0673,.1074]	[.2265,.2932]	[.46,.536]	
	Number of participants	168	86	245	463	962

Country		**Procalcitonin**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion	0.6316	0.0346	0.1856	0.1482	1
	(95%CI)	[.4766,.7634]	[.0049,.2068]	[.0854,.3573]	[.072,.2808]	
	Number of participants	58	1	8	8	75
Belgium	Proportion	0.7836	0	0.1321	0.0843	1
	(95%CI)	[.5667,.9093]		[.0343,.3947]	[.0287,.223]	

	Number of participants	44	0	3	4	51
Bulgaria	Proportion (95%CI)	0.44 [.0975,.8511]	0	0.12 [.0143,.5616]	0.44 [.0975,.8511]	1
	Number of participants	2	0	1	2	5
Croatia	Proportion (95%CI)	0.3887 [.226,.5807]	0.0601 [.0115,.2597]	0.3675 [.1995,.5753]	0.1837 [.0724,.3936]	1
	Number of participants	13	2	9	5	29
Cyprus	Proportion (95%CI)	0.4951 [.183,.8112]	0	0.3204 [.1108,.6408]	0.1845 [.0515,.4852]	1
	Number of participants	4	0	5	3	12
Czech Rep.	Proportion (95%CI)	0	0	1	0	1
	Number of participants	0	0	1	0	1
Denmark	Proportion (95%CI)	0.6857 [.1945,.9517]	0.3143 [.0483,.8055]	0	0	1

	Number of participants	4	1	0	0	5
Finland	Proportion	0.8228	0	0.0506	0.1266	1
	(95%CI)	[.6067,.9332]		[.0071,.2843]	[.04,.3354]	
	Number of participants	20	0	1	3	24
France	Proportion	0.5558	0	0.1351	0.3091	1
	(95%CI)	[.3409,.7517]		[.0409,.3637]	[.1423,.5468]	
	Number of participants	20	0	3	8	31
Germany	Proportion	0.7546	0.0368	0.0982	0.1104	1
	(95%CI)	[.5562,.883]	[.0089,.1398]	[.0198,.3702]	[.0493,.2293]	
	Number of participants	39	2	2	8	51
Greece	Proportion	0.4386	0.1244	0.1898	0.2472	1
	(95%CI)	[.3039,.583]	[.0534,.2636]	[.0972,.3377]	[.1295,.4203]	
	Number of participants	38	6	9	11	64
Hungary	Proportion	0.0593	0.1186	0.3559	0.4661	1

	(95%CI)	[.0081,.3281]	[.0171,.51]	[.1477,.638]	[.2233,.7261]	
	Number of participants	1	1	5	7	14
Ireland	Proportion	0.4667	0	0.3667	0.1667	1
	(95%CI)	[.0695,.9111]		[.0457,.8751]	[.0176,.6902]	
	Number of participants	1	0	1	1	3
Israel	Proportion (95%CI)	1	0	0	0	1
	Number of participants	2	0	0	0	2
Italy	Proportion	0.3658	0.0268	0.1745	0.4329	1
	(95%CI)	[.1434,.6651]	[.0061,.11]	[.0589,.4167]	[.2018,.6974]	
	Number of participants	7	2	6	12	27
Latvia	Proportion	0.9	0	0	0.1	1
	(95%CI)	[.6372,.9788]			[.0212,.3628]	
	Number of participants	7	0	0	2	9

Lithuania	Proportion (95%CI)	0.6667 [.3032,.9019]	0.0521 [.0066,.3136]	0.1771 [.025,.6438]	0.1042 [.0225,.3698]	1
	Number of participants	8	1	1	2	12
Malta	Proportion (95%CI)	0.3342 [.2013,.5]	0.1105 [.0413,.2639]	0.1078 [.0404,.2573]	0.4474 [.2974,.6077]	1
	Number of participants	13	4	4	18	39
Netherlands	Proportion (95%CI)	0.7135 [.5628,.8281]	0.0407 [.0089,.1671]	0	0.2458 [.1404,.3942]	1
	Number of participants	36	2	0	12	50
Norway	Proportion (95%CI)	0.6213 [.4789,.7454]	0.0653 [.0203,.1903]	0.166 [.0865,.2951]	0.1474 [.073,.2751]	1
	Number of participants	33	3	9	8	53
Poland	Proportion (95%CI)	0.0714 [.0246,.1898]	0.0728 [.0257,.1893]	0.0546 [.0192,.1459]	0.8011 [.6688,.8893]	1
	Number of participants	5	6	7	66	84

Portugal	Proportion (95%CI)	0.625 [.4519,.7711]	0.0402 [.0081,.1764]	0.125 [.0545,.2615]	0.2098 [.1095,.3645]	1
	Number of participants	26	2	8	12	48
Romania	Proportion (95%CI)	1	0	0	0	1
	Number of participants	7	0	0	0	7
Slovenia	Proportion (95%CI)	0.6677 [.4867,.8098]	0.0217 [.003,.1416]	0.1615 [.0745,.3154]	0.1491 [.0653,.3051]	1
	Number of participants	19	1	7	6	33
Spain	Proportion (95%CI)	0.4437 [.3234,.571]	0.0081 [.0011,.0561]	0.2469 [.1476,.3831]	0.3012 [.1945,.4349]	1
	Number of participants	37	1	13	19	70
Sweden	Proportion (95%CI)	0.41 [.1281,.7667]	0	0.12 [.0314,.3649]	0.47 [.1495,.8173]	1
	Number of participants	6	0	3	3	12

Switzerland	Proportion (95%CI)	0.6439 [.3801,.8421]	0	0.0634 [.0138,.2469]	0.2927 [.112,.5759]	1
	Number of participants	15	0	2	5	22
Ukraine	Proportion (95%CI)	0.4686 [.31,.6339]	0.0418 [.0167,.1009]	0.0816 [.0235,.2468]	0.4079 [.2627,.5713]	1
	Number of participants	22	5	4	22	53
UK	Proportion (95%CI)	0.6178 [.4942,.7279]	0.0611 [.0218,.1597]	0.0535 [.0195,.1381]	0.2675 [.1736,.3884]	1
	Number of participants	47	4	5	20	76
Total	Proportion (95%CI)	0.531 [.4928,.5689]	0.046 [.0328,.0641]	0.1351 [.1101,.1647]	0.2879 [.2544,.3239]	1
	Number of participants	534	44	117	267	962

Country	**Full blood count**

		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.1274 [.0661,.2314]	0.0762 [.0322,.1696]	0.277 [.1654,.4255]	0.5194 [.3812,.6547]	1
	Number of participants	12	7	21	35	75
Belgium	Proportion (95%CI)	0.2005 [.1091,.3392]	0.041 [.0101,.1515]	0.2961 [.1546,.4919]	0.4624 [.3094,.6228]	1
	Number of participants	13	2	12	24	51
Bulgaria	Proportion (95%CI)	0	0.12 [.0143,.5616]	0.32 [.0472,.8172]	0.56 [.1489,.9025]	1
	Number of participants	0	1	1	3	5
Croatia	Proportion (95%CI)	0.0318 [.0044,.196]	0.1201 [.0379,.3211]	0.4735 [.2902,.6642]	0.3746 [.2071,.5785]	1
	Number of participants	1	4	14	10	29
Cyprus	Proportion (95%CI)	0	0	0.8738 [.5795,.972]	0.1262 [.028,.4205]	1
	Number of participants	0	0	10	2	12
Czech Rep.	Proportion (95%CI)	0	0	1	0	1

	Number of participants	0	0	1	0	1
Denmark	Proportion (95%CI)	0	0	0.8 [.3025,.9736]	0.2 [.0264,.6975]	1
	Number of participants	0	0	4	1	5
Finland	Proportion (95%CI)	0.0802 [.0191,.2807]	0.0802 [.0191,.2807]	0.519 [.3211,.7111]	0.3207 [.1646,.5307]	1
	Number of participants	2	2	12	8	24
France	Proportion (95%CI)	0.5792 [.365,.7672]	0	0.2571 [.1114,.4887]	0.1636 [.0612,.3698]	1
	Number of participants	20	0	6	5	31
Germany	Proportion (95%CI)	0.2086 [.0902,.412]	0.0491 [.0157,.143]	0.4601 [.2744,.6576]	0.2822 [.1459,.475]	1
	Number of participants	10	4	19	18	51
Greece	Proportion (95%CI)	0.1021 [.0507,.1949]	0.2265 [.1253,.3743]	0.4577 [.3175,.6051]	0.2137 [.1069,.3817]	1
	Number of participants	10	12	29	13	64
Hungary	Proportion (95%CI)	0.0593 [.0081,.3281]	0	0.7034 [.435,.8796]	0.2373 [.0866,.5052]	1
	Number of participants	1	0	9	4	14

Ireland	Proportion	0.4667	0	0.3667	0.1667	1
	(95%CI)	[.0695,.9111]		[.0457,.8751]	[.0176,.6902]	
	Number of participants	1	0	1	1	3
Israel	Proportion	0	0	0.1579	0.8421	1
	(95%CI)			[.0115,.7508]	[.2492,.9885]	
	Number of participants	0	0	1	1	2
Italy	Proportion	0.2785	0	0.4329	0.2886	1
	(95%CI)	[.094,.5897]		[.2021,.697]	[.1076,.5771]	
	Number of participants	5	0	13	9	27
Latvia	Proportion	0.2889	0	0.3	0.4111	1
	(95%CI)	[.0603,.7202]		[.0744,.6957]	[.1306,.7644]	
	Number of participants	2	0	3	4	9
Lithuania	Proportion	0.0521	0	0.7396	0.2083	1
	(95%CI)	[.0066,.3136]		[.4325,.9137]	[.064,.5033]	
	Number of participants	1	0	7	4	12
Malta	Proportion	0.1509	0.1779	0.3181	0.3531	1
	(95%CI)	[.0681,.3019]	[.0855,.3336]	[.1874,.4854]	[.2176,.5172]	
	Number of participants	6	7	12	14	39
Netherlands	Proportion	0.488	0.0166	0.3216	0.1738	1
	(95%CI)	[.3448,.6332]	[.0023,.1098]	[.2003,.473]	[.0889,.3118]	

	Number of participants	24	1	16	9	50
Norway	Proportion (95%CI)	0.0448 [.0143,.1312]	0.0802 [.0331,.1817]	0.5672 [.4283,.6962]	0.3078 [.1968,.4467]	1
	Number of participants	3	5	28	17	53
Poland	Proportion (95%CI)	0.0042 [5.8e-04,.0297]	0.0462 [.0138,.1437]	0.1765 [.1007,.2907]	0.7731 [.6509,.8616]	1
	Number of participants	1	5	22	56	84
Portugal	Proportion (95%CI)	0.3259 [.1902,.4988]	0.058 [.0163,.1862]	0.3259 [.1751,.5241]	0.2902 [.1469,.4925]	1
	Number of participants	18	3	15	12	48
Romania	Proportion (95%CI)	0.1786 [.0253,.6455]	0	0.1071 [.0141,.5011]	0.7143 [.3168,.9309]	1
	Number of participants	1	0	1	5	7
Slovenia	Proportion (95%CI)	0.087 [.0127,.4136]	0.028 [.0039,.1759]	0.6366 [.4348,.7996]	0.2484 [.1303,.4219]	1
	Number of participants	1	1	21	10	33
Spain	Proportion (95%CI)	0.4464 [.3259,.5736]	0.0231 [.0032,.1461]	0.3392 [.2262,.4741]	0.1913 [.1057,.3215]	1
	Number of participants	38	1	20	11	70

Sweden	Proportion (95%CI)	0.28 [.0964,.5864]	0	0.51 [.1777,.8337]	0.21 [.0303,.6934]	1
	Number of participants	7	0	4	1	12
Switzerland	Proportion (95%CI)	0.3902 [.1824,.6475]	0.1073 [.0315,.3079]	0.3024 [.1202,.5791]	0.2 [.0806,.4164]	1
	Number of participants	7	3	6	6	22
Ukraine	Proportion (95%CI)	0.0816 [.0228,.2525]	0.2448 [.1301,.4126]	0.4623 [.306,.6265]	0.2113 [.1085,.371]	1
	Number of participants	3	14	24	12	53
UK	Proportion (95%CI)	0.1185 [.0606,.2186]	0.1949 [.1133,.3145]	0.3516 [.2454,.4748]	0.335 [.2318,.4569]	1
	Number of participants	10	13	27	26	76
Total	Proportion (95%CI)	0.1934 [.1655,.2247]	0.0844 [.0665,.1064]	0.3862 [.3495,.4243]	0.336 [.301,.3728]	1
	Number of participants	197	85	359	321	962

Country		**Blood gas analysis (with or without lactate)**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.331 [.2127,.4755]	0.0249 [.0051,.1138]	0.169 [.0807,.32]	0.4751 [.3409,.613]	1

	Number of participants	25	2	12	36	75
Belgium	Proportion (95%CI)	0.7267 [.5703,.8419]	0.0205 [.0028,.133]	0.0569 [.0135,.2098]	0.1959 [.1038,.3389]	1
	Number of participants	37	1	2	11	51
Bulgaria	Proportion (95%CI)	0.12 [.0143,.5616]	0.12 [.0143,.5616]	0.32 [.0472,.8172]	0.44 [.0975,.8511]	1
	Number of participants	1	1	1	2	5
Croatia	Proportion (95%CI)	0.5548 [.3605,.7336]	0.1095 [.0314,.3184]	0.1555 [.0575,.357]	0.1802 [.0773,.3658]	1
	Number of participants	16	3	4	6	29
Cyprus	Proportion (95%CI)	0.8058 [.4981,.9455]	0	0.068 [.0088,.3757]	0.1262 [.028,.4205]	1
	Number of participants	9	0	1	2	12
Czech Rep.	Proportion (95%CI)	1	0	0	0	1
	Number of participants	1	0	0	0	1
Denmark	Proportion (95%CI)	0	0	0.2857 [.0614,.7098]	0.7143 [.2902,.9386]	1
	Number of participants	0	0	2	3	5
Finland	Proportion	0.5232	0	0.3629	0.1139	1

	(95%CI)	[.3242,.7151]		[.1923,.5766]	[.0362,.3054]	
	Number of participants	13	0	8	3	24
France	Proportion	0.9143	0	0.0571	0.0286	1
	(95%CI)	[.7093,.979]		[.008,.3119]	[.006,.1258]	
	Number of participants	28	0	1	2	31
Germany	Proportion	0.362	0.0184	0.0429	0.5767	1
	(95%CI)	[.1967,.568]	[.0025,.1222]	[.0122,.1402]	[.3788,.7527]	
	Number of participants	19	1	3	28	51
Greece	Proportion	0.6507	0.0351	0.177	0.1372	1
	(95%CI)	[.4962,.779]	[.0068,.1624]	[.0858,.3302]	[.063,.2731]	
	Number of participants	46	2	8	8	64
Hungary	Proportion	0.2881	0.1186	0.0508	0.5424	1
	(95%CI)	[.1051,.5826]	[.0171,.51]	[.0069,.2931]	[.2776,.7852]	
	Number of participants	4	1	1	8	14
Ireland	Proportion	0.4667	0	0	0.5333	1
	(95%CI)	[.0695,.9111]			[.0889,.9305]	
	Number of participants	1	0	0	2	3
Israel	Proportion	1	0	0	0	1
	(95%CI)					
	Number of participants	2	0	0	0	2

Italy	Proportion (95%CI)	0.6678 [.4222,.8468]	0.0302 [.0068,.1234]	0.094 [.0168,.3864]	0.2081 [.09,.4111]	1
	Number of participants	14	2	2	9	27
Latvia	Proportion (95%CI)	0.8 [.3213,.9713]	0	0.2 [.0287,.6787]	0	1
	Number of participants	8	0	1	0	9
Lithuania	Proportion (95%CI)	0.8958 [.6302,.9775]	0	0	0.1042 [.0225,.3698]	1
	Number of participants	10	0	0	2	12
Malta	Proportion (95%CI)	0.345 [.2121,.5075]	0.0431 [.0106,.1596]	0.0377 [.0053,.223]	0.5741 [.4127,.7212]	1
	Number of participants	14	2	1	22	39
Netherlands	Proportion (95%CI)	0.9224 [.796,.9731]	0.0111 [.0015,.0755]	0.0259 [.0036,.1622]	0.0407 [.0089,.1671]	1
	Number of participants	46	1	1	2	50
Norway	Proportion (95%CI)	0.4851 [.3493,.6231]	0.0205 [.0029,.1322]	0.2687 [.1619,.4113]	0.2257 [.1324,.3578]	1
	Number of participants	25	1	14	13	53
Poland	Proportion (95%CI)	0.4118 [.2851,.5514]	0.0112 [.0026,.0464]	0.0784 [.0325,.1776]	0.4986 [.3631,.6343]	1

	Number of participants	39	2	9	34	84
Portugal	Proportion (95%CI)	0.9062 [.7831,.9628]	0	0.0089 [.0012,.0623]	0.0848 [.0314,.2096]	1
	Number of participants	42	0	1	5	48
Romania	Proportion (95%CI)	0.4643 [.1593,.7985]	0	0.1071 [.0141,.5011]	0.4286 [.1401,.7755]	1
	Number of participants	3	0	1	3	7
Slovenia	Proportion (95%CI)	0.8416 [.679,.9303]	0	0.0497 [.012,.1836]	0.1087 [.04,.2628]	1
	Number of participants	27	0	2	4	33
Spain	Proportion (95%CI)	0.635 [.5002,.7515]	0.0312 [.0067,.1331]	0.1289 [.0608,.2528]	0.2049 [.1166,.3348]	1
	Number of participants	49	2	7	12	70
Sweden	Proportion (95%CI)	0.67 [.2292,.9327]	0	0	0.33 [.0673,.7708]	1
	Number of participants	10	0	0	2	12
Switzerland	Proportion (95%CI)	0.9171 [.7435,.9769]	0	0	0.0829 [.0231,.2565]	1
	Number of participants	19	0	0	3	22
Ukraine	Proportion	0.6485	0.113	0.1234	0.1151	1

	(95%CI)	[.4794,.7871]	[.0408,.2763]	[.0506,.2712]	[.0447,.2654]	
	Number of participants	32	6	8	7	53
UK	Proportion (95%CI)	0.3503 [.2435,.4746]	0.042 [.0105,.1531]	0.0153 [.0021,.101]	0.5924 [.468,.7059]	1
	Number of participants	26	2	1	47	76
Total	Proportion (95%CI)	0.588 [.5504,.6247]	0.0289 [.0189,.044]	0.099 [.0786,.1239]	0.2841 [.2516,.3191]	1
	Number of participants	566	29	91	276	962

Country		**Lactate**				
		I would not use the test	I would use both POCT and lab versions of the test	I would use only the lab version of the test	I would use only the POCT version	Total
Austria	Proportion (95%CI)	0.8158 [.6739,.9047]	0	0.0346 [.0049,.2068]	0.1496 [.0739,.2793]	1
	Number of participants	65	0	1	9	75
Belgium	Proportion (95%CI)	0.795 [.5731,.9181]	0.0205 [.0028,.133]	0.1116 [.0231,.4006]	0.0729 [.022,.2154]	1
	Number of participants	45	1	2	3	51
Bulgaria	Proportion (95%CI)	0.44 [.0975,.8511]	0.12 [.0143,.5616]	0.12 [.0143,.5616]	0.32 [.0472,.8172]	1

	Number of participants	2	1	1	1	5
Croatia	Proportion (95%CI)	0.8622 [.6611,.9525]	0.0106 [.0014,.0736]	0.0989 [.0252,.3184]	0.0283 [.0039,.1775]	1
	Number of participants	25	1	2	1	29
Cyprus	Proportion (95%CI)	0.8738 [.5795,.972]	0.0583 [.0074,.3376]	0	0.068 [.0088,.3757]	1
	Number of participants	10	1	0	1	12
Czech Rep.	Proportion (95%CI)	1	0	0	0	1
	Number of participants	1	0	0	0	1
Denmark	Proportion (95%CI)	1	0	0	0	1
	Number of participants	5	0	0	0	5
Finland	Proportion (95%CI)	0.8397 [.6079,.9465]	0	0.1055 [.0268,.3356]	0.0549 [.0077,.3018]	1
	Number of participants	21	0	2	1	24
France	Proportion (95%CI)	0.8571 [.6341,.9541]	0	0.0571 [.008,.3119]	0.0857 [.021,.2907]	1
	Number of participants	27	0	1	3	31
Germany	Proportion	0.7791	0.0184	0.0184	0.184	1

	(95%CI)	[.5341,.9157]	[.0025,.1222]	[.0025,.1222]	[.0587,.4494]	
	Number of participants	45	1	1	4	51
Greece	Proportion	0.8246	0.0287	0.0383	0.1085	1
	(95%CI)	[.6805,.9121]	[.004,.1773]	[.0114,.121]	[.0427,.249]	
	Number of participants	55	1	3	5	64
Hungary	Proportion	0.661	0.1186	0	0.2203	1
	(95%CI)	[.3776,.8624]	[.0171,.51]		[.0793,.4812]	
	Number of participants	9	1	0	4	14
Ireland	Proportion	0.4667	0	0	0.5333	1
	(95%CI)	[.0695,.9111]			[.0889,.9305]	
	Number of participants	1	0	0	2	3
Israel	Proportion	1	0	0	0	1
	(95%CI)					
	Number of participants	2	0	0	0	2
Italy	Proportion	0.8423	0.0168	0.1141	0.0268	1
	(95%CI)	[.5948,.951]	[.0022,.1163]	[.025,.393]	[.0061,.11]	
	Number of participants	22	1	2	2	27
Latvia	Proportion	0.4889	0	0.2	0.3111	1
	(95%CI)	[.1691,.8181]		[.0287,.6787]	[.0781,.7066]	
	Number of participants	6	0	1	2	9

Lithuania	Proportion (95%CI)	0.9479 [.6864,.9934]	0	0	0.0521 [.0066,.3136]	1
	Number of participants	11	0	0	1	12
Malta	Proportion (95%CI)	0.628 [.4623,.7683]	0	0.0997 [.0322,.2693]	0.2722 [.1545,.4337]	1
	Number of participants	25	0	3	11	39
Netherlands	Proportion (95%CI)	0.8854 [.7537,.9512]	0	0	0.1146 [.0488,.2463]	1
	Number of participants	44	0	0	6	50
Norway	Proportion (95%CI)	0.8526 [.7153,.9302]	0.0205 [.0029,.1322]	0.0821 [.0266,.2267]	0.0448 [.0143,.1312]	1
	Number of participants	46	1	3	3	53
Poland	Proportion (95%CI)	0.7577 [.6278,.8529]	0.0644 [.0225,.1711]	0.0728 [.0257,.1893]	0.105 [.0514,.2028]	1
	Number of participants	61	5	6	12	84
Portugal	Proportion (95%CI)	0.9063 [.7446,.9698]	0	0	0.0937 [.0302,.2554]	1
	Number of participants	45	0	0	3	48
Romania	Proportion (95%CI)	1	0	0	0	1

	Number of participants	7	0	0	0	7
Slovenia	Proportion (95%CI)	1	0	0	0	1
	Number of participants	33	0	0	0	33
Spain	Proportion (95%CI)	0.7368 [.6001,.8393]	0.0543 [.0163,.1661]	0.0719 [.0259,.1843]	0.137 [.0655,.2647]	1
	Number of participants	56	3	4	7	70
Sweden	Proportion (95%CI)	0.71 [.2289,.9528]	0	0	0.29 [.0472,.7711]	1
	Number of participants	11	0	0	1	12
Switzerland	Proportion (95%CI)	0.9366 [.7531,.9862]	0	0	0.0634 [.0138,.2469]	1
	Number of participants	20	0	0	2	22
Ukraine	Proportion (95%CI)	0.659 [.4908,.7948]	0.0167 [.0041,.0663]	0.0418 [.0144,.1154]	0.2824 [.1558,.4564]	1
	Number of participants	34	2	4	13	53
UK	Proportion (95%CI)	0.549 [.4273,.6652]	0.0191 [.0027,.1235]	0.0153 [.0038,.0598]	0.4166 [.3034,.5393]	1
	Number of participants	42	1	2	31	76
Total	Proportion	0.784	0.0209	0.0489	0.1463	1

	(95%CI)	[.7502,.8143]	[.0126,.0344]	[.0337,.0704]	[.121,.1757]	
	Number of participants	776	20	38	128	962

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Chapter 5: (Research Paper 2) The adoption of C-reactive protein rapid tests in primary care in the Netherlands and England: a comparative health systems analysis

5.1. Introduction

This chapter addresses Objective 3 of the thesis and aims to provide an in-depth understanding of the factors that contribute to the high versus low availability of CRP POCTs in two countries with different levels of availability, and to explore whether the tests are used in children.

This research paper was accepted for publication by BMC Health Services Research in January 2023. The manuscript and supplementary materials are presented in the following sections.

5.2. Citation

Dewez JE, Nijman RG, Fitchett EJA, Lynch R, et al. Adoption of C-reactive protein point-of-care tests for the management of acute childhood infections in primary care in the Netherlands and England: a comparative health systems analysis. BMC Health Serv Res. 2023;23(1):191.

5.3. Cover sheet

The Research Paper Cover Sheet is enclosed in the following pages.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	210537	**Title**	Dr
First Name(s)	Juan Emmanuel		
Surname/Family Name	Dewez		
Thesis Title	The adoption of rapid diagnostic tests for the clinical management of acute childhood infections in European settings.		
Primary Supervisor	Professor Shunmay Yeung		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The manuscript was submitted to BMC Health Services, and was accepeted for publication in January 2023.
Please list the paper's authors in the intended authorship order:	Juan Emmanuel Dewez, Ruud G. Nijman, Elizabeth Fitchett, Rebecca Lynch, Ronald de Groot, Michiel van der Flier, Ria Philipsen, Harriet Vreugdenhil, Stefanie Ettelt, Shunmay Yeung.
Stage of publication	In press

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study with my primary supervisor. I developed the protocol and study materials, and obtained ethical approval, with inputs from my primary supervisor and the co-authors. I conducted the document review and all the qualitative interviews (one interview was conducted with my supervisor). I managed and cleaned the data arising from the study. I conducted the thematic analyses with inputs from Elizabeth Fitchett at an early stage, and then from all co-authors. I drafted the manuscript which was reviewed and edited by all co-authors. I submitted the manuscript.

SECTION E

Student Signature	
Date	17 January 2023

Supervisor Signature	
Date	17 January 2023

5.4. Abstract

Background

The use of point of care tests (POCTs) varies across Europe, but research into what drives this variability is lacking. Focusing on CRP POCTs, we aimed to understand what factors contribute to high versus low adoption of the tests, and also to explore whether they are used in children.

Methods

We used a comparative qualitative case study approach to explore implementation of CRP POCTs in the Netherlands and England. These countries were selected because although they have similar primary healthcare systems, the availability of CRP POCTs in General Practices is very different, being very high in the former and rare in the latter. The study design and analysis were informed by the non-adoption, abandonment, spread, scale-up and sustainability (NASSS) framework. Data were collected through a review of documents and interviews with stakeholders. Documents were identified by a scoping literature review, search of websites, and stakeholder recommendation. Stakeholders were selected purposively initially, and then by snowballing. Data were analysed thematically.

Results

Sixty-five documents were reviewed, and 21 interviews were conducted. The difference in the availability of CRP POCTs is mainly because of differences at the wider national context level. In the two countries, early adopters of the tests advocated for their implementation through the generation of robust evidence and by engaging with all relevant stakeholders. This led to the inclusion of CRP POCTs in clinical guidelines in both countries. In the Netherlands, this mandated their reimbursement in accordance with Dutch regulations. Moreover, the prevailing better integration of health services enabled operational support from laboratories to GP practices. In England, the funding constraints of the National Health Service and the prioritization of alternative and less expensive antimicrobial stewardship interventions prevented the development of a reimbursement scheme. In addition, the lack of integration between health services limits the operational support to GP practices. In both

countries, the availability of CRP POCTs for the management of children is a by-product of the test being available for adults. The tests are less used in children mainly because of concerns regarding their accuracy in this age-group.

Conclusions

The engagement of early adopters combined with a more favourable and receptive macro level environment, including the role of clinical guidelines and their developers in determining which interventions are re-imbursed, and the operational support from laboratories to GP practices, led to the greater adoption of the tests in the Netherlands. In both countries CRP POCTs, when available, are less used less in children. Organizations considering introducing POCTs into primary care need to consider how their implementation fits into the wider health system context to ensure achievable plans.

Key Words

Comparative health systems analysis, NASSS framework, C-reactive protein, point-of-care tests, the Netherlands, England, acute childhood infections, primary care.

5.5. Manuscript

5.5.1. Background

Fever is a common reason for paediatric consultations in primary care.[1] Most febrile children have self-limiting infections,[2,3] but differentiating the few febrile children with severe bacterial infections from those with minor illness is difficult because the clinical features of infection in children are often non-specific. The resulting diagnostic uncertainty combined with avoidance of risk lead to the over-prescription of antibiotics,[4] which may contribute to antimicrobial resistance.[5]

Point-of-care tests (POCTs) have been widely advocated to reduce antibiotic resistance.[5] They can be easily performed in the consultation room, provide rapid results, and may optimise antibiotics use and patient care.

Few POC tests are used in the clinical management of acute fever in children, and their performance and impact seem to vary.[6] These include urine dipsticks to diagnose urinary tract infections, rapid throat tests to identify Group A Streptococcal infections, and C-reactive protein (CRP) POCTs.

CRP is a non-specific marker of acute inflammation used to indicate the severity of infections.[7] It is one of the most widely used and studied biomarkers in the management of infections.[8] The clinical accuracy and effectiveness of using CRP POCTs in primary care have been studied extensively, mainly in the management of adults. Recent systematic reviews have concluded that the use of the tests can help to reduce antibiotic prescription in adults with respiratory tract infections. With regards the use of the tests in children, it also reduces antibiotic prescription, but only if guidance is provided.[9-10] However, the cost-effectiveness of using CRP POCTs and the broader factors that influence their implementation in routine practice, such as clinicians' attitudes, funding, quality assurance, impact on workload, or regulation,[9,11] have received less attention.[12] The availability of CRP POCTs in primary care varies across Europe with higher availability in Scandinavian countries, Switzerland, and the Netherlands compared to England or other countries.[13,14] Moreover, whether CRP POCTs are used in the management of acute childhood infections is unclear.

Understanding the mechanisms that influence the availability and use of CRP POCTs is important to inform the implementation of current and future POCTs for the management of acute childhood infections. The aims of this study were to generate an in-depth understanding of the factors that contribute to a high versus a low availability of CRP POCTs in two countries with similar primary healthcare systems, and to explore whether the tests are used in children.

5.5.2. Methods

A comparative qualitative analysis based on two country case studies of the implementation of CRP POCTs was conducted. This approach was chosen as it allows for in-depth understanding of a multifaceted phenomenon such as the introduction of diagnostics which involves multiple actors and processes within a wider national context through a comparative lens. The design of the study was informed by the non-adoption, abandonment, spread, scale-up and sustainability of healthcare technologies (NASSS) framework.[15] The NASSS framework was developed to identify factors that contribute to the adoption of innovations in healthcare services by assessing the complexity of seven domains: (1) the condition or illness; (2) the technology; (3) the value of the innovation for developers and users; (4) the adopters and whether the innovation implied a change in their identity and practices; (5) the organisations where the innovation is implemented, whether they are ready for this innovation, how the innovation changes the organisations' routines, and the work needed to adopt, fund, and normalise the innovation; (6) the wider context including the policy and regulatory contexts, the role of professional bodies and interorganisational networking; and (7) the adaptation of the innovation, its use, and the healthcare organisations over time (Figure 21).

The two countries that were purposively selected for the comparison were the Netherlands and England. The criterion used to make this selection was to allow for a "more similar" type of comparison,[16] i.e., the countries where there is a substantial difference in the outcome of interest (high availability of CRP POCTs in primary care in the Netherlands and very low in England),[13,17] but where the context are similar with regards the organisation of primary care services and in the overall share of the country wealth that is invested in healthcare. In both countries general practitioners (GPs) provide primary care for children, are the gatekeepers

of health services, and health expenditure is similar at around 10% of GDP.[18] An additional criterion was feasibility in terms of working within an established collaboration.

Data were collected through an iterative process combining document analysis and interviews with stakeholders. The initial document analysis sought to explore the wider health system contexts and to inform the identification of relevant stakeholders and the development of topic guides (supplementary materials 1). This was followed by interviews of stakeholders and additional document analyses. The iterative combination of these two methods allowed triangulation of data for two purposes: (1) to cross-validate findings and (2) to extend the understanding of findings.

Documents were included if they pertained to the adoption of CRP POCTs in the two countries and were published after 2000. Documents included publications in medical journals, clinical guidelines, information for patients, information for implementors of diagnostic tests, reports from healthcare organisations, minutes of meetings, and proceedings of conferences. Documents were identified through a multi-pronged approach: a scoping review of the literature; an extensive search of the websites of relevant healthcare organisations; interviewee recommendations; and through attendance at relevant meetings (see supplementary materials 2 for additional details).

Stakeholders were selected based on their expert knowledge of at least one domain of the NASSS framework pertaining to the adoption of CRP POCTs in primary care in their country. We also ensured that we had at least one representative of the three levels of health systems: micro (stakeholders who used/could use CRP POCTs), meso (stakeholders directly involved in the implementation of diagnostics in GP practices) and macro (stakeholders involved in the wider national context). Based on the inclusion criteria, potential interviewees were identified through personal contacts, searching authors of relevant reports, and in the UK by attending relevant conferences. Initial interviewees were sampled purposively followed by snowball sampling to identify additional stakeholders that could provide insights on domains of the NASSS framework that were not covered in initial interviews.

In the Netherlands, the interviewees were based in Nijmegen where the members of the research team worked, and in Eindhoven, Leusden and Utrecht. In England, interviewees

worked in Hertfordshire, Herefordshire, Southampton, and London. Potential participants were contacted by email or telephone to ascertain their interest in being interviewed. Those who agreed, were followed-up by JED who provided a participant information sheet, obtained written informed consent, and arranged the interview date.

JED conducted all the interviews, with SY participating in one interview in the Netherlands. The interviewers did not know participants beforehand. Face-to-face audio recorded interviews took place at the respondents' workplace between March 2019 and February 2020, and by videoconference between March 2020 and August 2021 because of the restriction due to the COVID-19 pandemic. Only the interviewers and the participants were present during the interview. All interview records were transcribed verbatim by a research assistant or JED. Field notes were taken after each interview. One transcript was returned to a participant who requested this; no corrections were made. Two participants were recontacted to clarify the information provided in the interviews. No repeat interviews were conducted.

The documents and interview transcripts were analysed thematically. The analysis was deductive based on the seven domains of the NASSS framework. JED extracted data from the interview transcripts and documents and collated them per NASSS domain using matrices in Excel, including alternative views, when available. EF independently assessed whether each extract was assigned to the most relevant NASSS domains. Discrepancies were resolved through discussion and consensus between JED and EF. Data from the two countries were analysed separately. A summary of each domain was produced and the summaries of the two countries were then compared descriptively to highlight similarities and differences for each domain. All authors verified the consistency of each domain summary. Data saturation was considered reached when all domains of the NASSS framework were covered and each domain was clearly understood. Participants did not provide feedback on the findings.

5.5.3. Results

Sixty-five documents including research publications, clinical guidelines, reimbursement decisions, health systems reviews, and policies were included in the analysis (Table 6).

Table 6. Documents included in the analysis about the adoption of CRP POCTs in primary care

Author and year	Title	Type of document	NASSS domains
Hay, 2005[1]	The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children.	Observational study aiming to describe symptom and consultation prevalence in pre-school children.	Domain 1
de Bont, 2015[19]	Workload and management of childhood fever at general practice out-of-hours care.	Observational study aiming to describe the work of out of hours GPs.	Domain 1 and 5
Veldhoen, 2009[20]	Changes in infectious disease mortality among children in the Netherlands.	Observational study aiming to examine the changes in mortality due to infectious diseases in childhood over recent decades in the Netherlands.	Domain 1
Pearson, 2008[21]	Why Children Die: A Pilot Study.	Confidential Enquiry into Maternal and Child Health.	Domain 1
Kool, 2015[22]	Febrile children at a general practice out-of-hours service.	PhD thesis on the management of fever in children in GP practices.	Domain 1
Morley, 1991[23]	Field trials of the Baby Check score card in general practice.	Observational study aiming to assess the efficacy of a tool to identify children at risk of severe disease.	Domain 1
Hjortdahl, 1991[24]	C-Reactive Protein: A New Rapid Assay for Managing Infectious Disease in Primary Health Care.	Diagnostic test accuracy study of CRP.	Domain 2
O'Brien, 2019[25]	CRP POCT to guide antibiotic prescribing in primary care settings for acute respiratory tract infections.	Health technology assessment of CRP POCT.	Domain 2 and 6
Hopstaken, 2003[26]	Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection.	Diagnostic test accuracy study of CRP.	Domain 2
Van Vugt, 2013[27]	Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study.	Diagnostic test accuracy study of CRP.	Domain 2

Minaard, 2015[28]	The added diagnostic value of five different C-reactive protein point-of-care test devices in detecting pneumonia in primary care.	Diagnostic test accuracy study of CRP POCT.	Domain 2
Van den Bruel, 2011[29]	Diagnostic value of laboratory tests in identifying serious infections in febrile children.	Systematic review of the diagnostic test accuracy of various biomarkers including CRP to predict serious bacterial infections.	Domain 2
Kool, 2016[30]	C-Reactive Protein level as diagnostic marker in young febrile children presenting in a general practice out-of-hours service.	Diagnostic test accuracy study of CRP POCT.	Domain 2
NHG, 2011[31]	NHG Guidelines for acute cough.	Guidelines from the Dutch college of GPs on cough.	Domain 2
NHG b, 2011[32]	NHG Guidelines on diverticulitis.	Guidelines from the Dutch college of GPs on diverticulitis.	Domain 2
NHG, 2021[33]	NHG Guidelines on Chronic Obstructive Pulmonary Disease.	Guidelines from the Dutch college of GPs on COPD.	Domain 2
NICE, 2014[34]	NICE Clinical guideline on pneumonia in adults: diagnosis and management.	National Institute for Health and Care Excellence's guidelines for the management of pneumonia.	Domain 2, 3, and 6
Howick, 2014[13]	Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA.	Survey about the availability of POCT tests in primary care.	Domain 3
Kip, 2019[17]	Understanding the adoption and use of point-of-care tests in Dutch general practices using multi-criteria decision analysis.	Case study to guide POC test development and their introduction in clinical practice.	Domain 3
Cals, 2009[35]	Effect of point of care testing for C- reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections.	Randomised trial to assess the efficacy of CRP POCT to reduce antibiotic prescription in primary care.	Domain 3
Cals, 2010[36]	Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections.	Randomised trial to assess the efficacy of CRP POCT to reduce antibiotic prescription in primary care.	Domain 3
Little, 2013[37]	Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial.	Randomised trial to assess the efficacy of CRP POCT to reduce antibiotic prescription in primary care.	Domain 3

Weesie, 2017[38]	CRP point of care testing and prescribing antibiotics at the GP post.	Before-and-after evaluation of the use of CRP POCT in primary care.	Domain 3
Little, 2019[39]	Antibiotic Prescribing for Acute Respiratory Tract Infections 12 Months After Communication and CRP Training: A Randomized Trial.	Long term analysis of a randomised trial on the effectiveness of CRP POCT to reduce antibiotic prescription.	Domain 3
Cals, 2011[40]	C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial.	Cost-effectiveness analysis of C-Reactive Protein POCT to reduce antibiotic prescribing in primary care.	Domain 3
Holmes, 2018[41]	Cost-Effectiveness Analysis of the Use of Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing in Primary Care.	Cost-effectiveness analysis of C-Reactive Protein POCT to reduce antibiotic prescribing in primary care.	Domain 3
Kroneman, 2016[42]	The Netherlands Health system review.	In-depth review of the Dutch health system.	Domain 5 and 6
Cylus, 2015[43]	United Kingdom Health system review	In-depth review of the British health system.	Domain 5 and 6
UK Government, 2014[44]	International comparisons of selected service lines in seven health systems.	Case study describing GP posts in the Netherlands.	Domain 5 and 6
Mossialos, 2017[44]	International profiles of healthcare systems, 2016.	In-depth review of the Dutch health system.	Domain 5 and 6
Mguire, 2011[46]	Which urgent care services do febrile children use and why?	Observational study aiming to explore how parents navigate urgent and emergency care services when their child <5 years old has a feverish illness	Domain 5 and 6
Wolfe, 2016[47]	Child Health Systems in the United Kingdom (England)	In-depth review of child health services in England.	Domain 5 and 6
Bentum, 2018[48]	Determining factors that influence purchasing laboratory services in primary care.	MSc dissertation	Domain 5
NVKC, 2015[49]	Guidelines: Point of care testing (POCT) in general practice.	Dutch College of GPs and the Dutch Association for Clinical Chemistry and Laboratory Medicine guidelines for the use of POCT tests in primary care.	Domain 5
NHS, 2020[50]	Diagnostics recovery and renewal.	Independent review of the diagnostic services for NHS England.	Domain 5 and 7

Wammes, 2020[51]	International Health Care System Profiles: Netherlands	In-depth review of the Dutch health system.	Domain 5
Nuffield trust, 2014[52]	The NHS payment system: evolving policy and emerging evidence.	Independent review of the NHS payment system.	Domain 5
NHS England, 2020[53]	Delegated commissioning of primary medical services.	NHS England website.	Domain 5
UKADC, 2018[54]	CRP & POC Accelerated Learning Workshop 2018	Workshop organised by NHS England to explore facilitators and barriers to the implementation of CRP POCT in the NHS	Domain 5
Dutch government, 2015[55]	Tackling antimicrobial resistance, the Dutch one health approach.	Summary of the Dutch antibiotic resistance policy.	Domain 6
ECDC, 2019[56]	Antimicrobial consumption in the EU/EEA	Report on trends in antimicrobial consumption for systemic use in the community (primary care sector) in Netherlands, United Kingdom from 1997 to 2019	Domain 6
UK government, 2013[57]	UK 5-year antimicrobial resistance strategy 2013 to 2018.	British antimicrobial resistance plan.	Domain 6
Anyanwu, 2019[58]	Conceptualising the Integration of Strategies by Clinical Commissioning Groups in England towards the Antibiotic Prescribing Targets for the Quality Premium Financial Incentive Scheme: A Short Report	Qualitative study reporting antimicrobial stewardship measures used by CCGs.	Domain 6
van der Linden, 2001[59]	Integration of care in The Netherlands: the development of transmural care since 1994.	National survey to determine the success of the bottom-up policy and the extent of the development of transmural care.	Domain 6
Maile, 2022[60]	Back to the future? Lessons from the history of integrated child health services in England.	Review of the history of integration in the English National Health Service.	Domain 6
European Commission, 2021[61]	CE marking.	Information on the European Union's single market standards.	Domain 6
UK Accreditation Standards, 2022[62]	Point of care testing accreditation.	UK standard for POC accreditation	Domain 6
NZA, 2011[63]	Decisions of the Board of Directors October 11, 2011.	Official decision by the Dutch Health Authority to include CRP POCT in the list of reimbursable consumables.	

Thomson, 2020[64]	Private Health Insurance history politic and performance	In-depth review of the private health insurance schemes	Domain 6
European Commission, 2016[65]	The Netherlands Health Care & Long-Term Care Systems.	In-depth review of the Dutch health systems by the European Commission.	Domain 6
Borisenko, 2018[66]	Innovative payment schemes for medical technologies and in- vitro diagnostic tests in Europe.	Report by the European invitro diagnostic industry association about reimbursement schemes.	Domain 6
Derksen, 2011[67]	Medical tests (assessment of established medical science and medical practice).	Processes for the evaluation of diagnostics by the Zoorg Institute Netherlands.	Domain 6
Thomson, 2009[68]	Financing healthcare in the European Union.	In-depth review of financing mechanisms for healthcare	Domain 6
Anderson, 2021[69]	Re-laying the foundations for an equitable and efficient health and care service after COVID-19	LSE-Lancet Commission on the future of the NHS.	Domain 6
OECD, 2020[18]	Health spending, 2020.	Report on health spending in countries member of the Organisation for Economic Cooperation and Development.	Domain 6
Steel, 2018[70]	Changes in health in the countries of the UK and 150 English Local Authority areas 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.	Systematic analysis of the burden of disease in the UK.	Domain 6
ROS Robuust 2021[71]	ROS Robuust.	Website of regional support organization	Domain 6
AHSN, 2021[72]	Academic Health Science Network.	Website of national support organization	Domain 6
Van den Bruel, 2016[73]	C-reactive protein point-of-care testing in acutely ill children: a mixed methods study in primary care.	Randomised clinical trial in England.	Domain 6
UKADC, 2021[74]	United Kingdom Antimicrobial Diagnostics Collaboration	Website of public institution supporting the implementation of diagnostics.	Domain 6
Johnson, 2018[75]	Funding and policy incentives to encourage implementation of point-of-care C-reactive protein testing for lower respiratory tract infection in NHS primary care: a mixed-methods evaluation.	Implementation research study about the the introduction of a reimbursement scheme for the adoption of CRP POC tests.	Domain 6
Eley, 2020[76]	Effects of primary care C-reactive protein point-of-care testing on antibiotic prescribing by general practice	Randomised clinical trial in England.	Domain 6

	staff: pragmatic randomised controlled trial, England, 2016 and 2017.		
Wakeman, 2018[77]	Point-of-care C-reactive protein testing in community pharmacy to deliver appropriate interventions in respiratory tract infections (RTIs)	Study investigating the feasibility of a rural community pharmacy offering this service and delivering the most appropriate intervention in RTIs.	Domain7
Zorginstituut, 2019[78]	Report initial meeting Sensible Care Lower respiratory tract infection and pneumonia.	Minutes of the meeting of the Zoorg Institute working group assessing the quality of primary care	Domain 7
Review on Antimicrobial Resistance, 2015[79]	Rapid diagnostics: stopping unnecessary use of antibiotics. The review on antimicrobial resistance.	Independent review on antimicrobial resistance commissioned by the UK government.	Domain 7

A total of 21 stakeholders were interviewed, including GPs, POCT implementors (i.e., the head of a laboratory implementing POCTs in primary care, and a nurse in charge of implementing a pilot study with CRP POCTs) and representatives of a Clinical Commissioning Group, a health insurance company, NHS improvement (a professional body supporting quality improvement in the English National Health Service), clinical guideline development bodies, and the in-vitro diagnostics industry (Table 7). All the included GPs from the Netherlands used CRP POCTs because despite our efforts we were unable to identify GPs who did not; in England four of the six GPs had used the test as part of pilot studies. Three GP practices did not reply to the invitation: one in the Netherlands and two in England. Four successive industry representatives did not reply to the invitation in England. Interviews lasted 32-73 minutes.

Table 7. Characteristics of stakeholders

Stakeholders	Netherlands	England
In vitro diagnostics industry representatives	1 (F)	1 (M)
Health insurance company representative	1 (M)	-
Clinical commissioning group member	-	1 (M)
Clinical guidelines development group member	1 (M)	1 (M)
Member of NHS quality improvement programme (NHS Improvement)	-	1 (F)
CRP POCT tests implementors in primary care	1 (M, head of hospital laboratory)	1 (F, Nurse Practitioner)
General practitioners		
Consultants	4 (2F)	5 (1F)
Trainees	2 (1F)	1 (F)
Total	**10**	**11**

F: Female; M: Male

The analysis identified similarities and differences in the seven NASSS domains between the two countries (Table 8) and are presented narratively below. In the narrative we intertwined data from the documents and the interviews pertaining to each domain of the NASS framework to synthesise the findings.

5.5.3.1. The condition

The condition is acute fever in children. There are few differences between the two countries regarding the burden of the condition in primary care. Fever in children usually indicates the presence of infection and is a common cause of consultation, with estimates of around 31 % of children consulting for fever in primary care in the Netherlands,[19] and 20-39 % in England.[1] Infections are one of the leading causes of death in children, with 23% and 20% of child deaths caused by infections in the Netherlands[20] and in England,[21] respectively. However, <5% and 3.5 % of children presenting to primary care services are estimated to have severe infections in the Netherlands[22] and in England,[23] respectively.

In both countries, most of the interviewed GPs expressed concern about missing severe infections in children:

"We send too many children to a paediatrician because we are just afraid to miss one case of severe infection" (GP3-Netherlands).

"[We are]…very, very careful (with children)" (GP4-England).

5.5.3.2. The technology

Material features and type of data generated

CRP POCTs were initially developed in Norway[24] and Finland.[25] They are available as a quantitative or a semi-quantitative test. We only considered the quantitative devices, as these are the devices implemented in the two countries and that are the object of the documents included in this study. There are currently twelve quantitative CRP tests available.[25] They are cartridge-based tests where a droplet of blood, usually obtained by finger prick, is placed in a cartridge that is then inserted into a small mains-powered analyser.

Table 8. Summary of differences in the NASSS domains that explain the difference in adoption of CRP POCTs in primary care between the Netherlands and England

Domains	Summary of differences between countries (Green: minor differences; amber: moderate differences; red: major differences)
1. The condition (acute fever in children)	• The burden of acute fever in children and the concern of missing potentially severe infections are similar in both countries.
2. The technology (CRP POCT tests)	• The technology, the perception of its functionality and dependability are similar in both countries. • Most participants in both countries thought that the test was not perfect but accurate enough for the management of respiratory infections in adults, but had reservations regarding the accuracy of the test in children • Healthcare providers have sufficient knowledge and skills to learn to use the test in both countries.
	• No guidelines recommend the use of CRP POC tests in children in primary care in both countries. • Three guidelines recommend the use of POC tests in primary care in adults (for the management of cough, suspicion of diverticulitis, and COPD exacerbation) in the Netherlands; In England one guideline recommended the use of the tests in adults for the management of pneumonia.
	• The commercial supply models are similar in both countries.
3. The value of CRP POCT tests for developers, users, and patients	• In the Netherlands, POC tests in general were perceived as a technology worth investing in, while in England there were more doubts because POC tests were perceived as difficult to commercialise.
	• There was a variety of views regarding the value of CRP POC tests for GPs with no specific pattern per country. Common values were that they help support clinical decisions (such as antibiotic prescription) and improve communication with patients.
	• The use of CRP POCT tests in adults with cough was found to be cost-effective in the two countries. There are no cost-effectiveness studies about the use of the test in febrile children. • GPs reported a variety of parental and child perceptions about the value of CRP POCT tests, ranging from patients asking for the tests to be performed to patients mistrusting the tests.
4. The adopters	• CRP POCT tests did not change the identities and roles of healthcare workers and usually did not change existing pathways inside the GP practices in both countries.
	• The disruption caused by the extra time to provide explanations about CRP POC tests or to review patients if the test was not normal was perceived as worsening the perceived high workload by some GPs in England.

	• In both countries most GPs use CRP POC tests when made available, but the tests are substantially less used in children than in adults, because of the perceived lack of accuracy, the absence of guidelines and the perceived invasiveness of finger pricking in children. • In both countries, most GPs reported that patients and carers usually accept the tests if the GP decides to use them.
5. The organisations (GP practices)	• GP practices are businesses owned by GP partners and are the recommended first point of care for acute infections in both countries. • The willingness to adopt innovations varied across practices with no specific pattern per country.
	• GP practices have less capacity to implement Innovations in England because of the perceived high workload of healthcare providers, and funding constraints.
	• The partial re-imbursement of CRP POC tests via a fee-for-service scheme and the better integration within and between primary and secondary care, which allowed for an effective operational support from laboratories to GP practices facilitated the adoption of CRP POC tests in the Netherlands.
6. The wider context	• AMR policies in the Netherlands did not recommend the use of POC tests. In England, AMR policies recommended the use of POC tests but not CRP POC tests specifically.
	• In the Netherlands, policies supporting the integration of health services, might have laid the foundation for the operational support of laboratories to GP practices. Integration of health services is less developed in England, and commissioning of diagnostic tests is fragmented.
	• The same regulatory standards are in use in the two countries
	• The inclusion of CRP POC tests in guidelines of the Dutch College of GPs in the Netherlands mandated the reimbursement of the tests as per Dutch regulations. In England, NICE guidelines had no legal power on the implementation of diagnostics. • In England, the funding constraints of the National Health Service led commissioners of healthcare to prioritise interventions addressing the burden of non-communicable diseases and other cheaper antimicrobial stewardship programmes.
	• In both countries, early adopters of the tests advocated for their implementation through the generation of robust evidence and by engaging with all relevant stakeholders.
7. Adaptation of the technology over time	• In both countries some GPs have adapted their practice over time and use the tests outside of the recommendations of current guidelines, including in children.

CRP: C-reactive protein; POCT: point-of-care test; GPs: general practitioners; COPD: chronic obstructive pulmonary disease; NICE: National Institute for Health and Care Excellence.

The results are usually available within five minutes and displayed as digital read out of blood CRP concentration in mg/L.

The accuracy of CRP POCTs varies according to the condition for which the test is used;[25] Several studies found that the accuracy of CRP in the management of low respiratory tract infection in adults is good, although not perfect.[26-28] With regards the accuracy in febrile children, CRP is one of the best biomarkers to identify severe infections in children.[29] However, the accuracy of rapid CRP POCTs in febrile children in primary care settings is still debated.[30] In this study, GPs reported using the tests mainly for managing adults with cough and were more uncertain about the accuracy of the test in children:

"I am not quite so convinced that a normal CRP would mean they actually are quite well, they don't have a bacterial infection" (GP3-England).

Knowledge and support to use the tests

Most participants in both countries thought that the tests were quick and easy to use:

"Much easier (than venous sampling), it's quicker, it's simple, it's clean" (GP2-Netherlands)

"To get the test back in four minutes is fantastic" (GP1-England).

Ideally, the use and interpretation of results should be informed by clinical guidelines. Guidelines from the Dutch Royal College of GPs recommend the use of CRP POCTs for the management of adults with cough,[31] suspected diverticulitis,[32] and exacerbation of COPD.[33] The tests are only recommended in patients with diagnostic uncertainty to help in deciding whether antibiotics should be prescribed. In England, one guideline from the National Institute for Health and Care Excellence (NICE) recommends the use of CRP POCTs in adults with suspected pneumonia which is similar to the Dutch equivaltent.[34] In both countries, there are no guidelines that recommend the use of CRP POCTs in primary care in children.

Support of actual implementation of the tests is covered in section 5.5.3.5.

Adaptation of the technology and supply model

The implementation of POCTs is complex and involves several actors and processes (see sections 5.5.3.4, 5.5.3.5, and 5.5.3.6) but from a technological point of view, CRP POCTs are relatively straightforward devices that do not need to be specifically adapted prior to their implementation in any healthcare facility.

Some of the manufacturers of the tests are large multinational companies[25] which supply both the Netherlands and England. This means that the tests can be purchased and obtained in the two countries in similar ways.

5.5.3.3. The value proposition

In the Netherlands, the availability of CRP POCTs in GP practices is high with estimates of between 48 %[13] and 80%[17] in 2014-2015. By contrast, the availability of CRP POCTs in GP practices in England is much lower but data are scanty. One survey conducted in 2014 reported availability to be 15% in 2014.[13]

The potential "value" of the test depends on the perspective i.e., whether it is the perspective of industry ("supply-side") or individual GPs, or health care commissioners ("demand-side").

Supply-side value

From the perspective of the in-vitro diagnostic industry, there is revenue potential in Netherlands:

"Everybody says that they expect that it is becoming more and more, popular, and that the growth in diagnostic industry will be in point of care and not in lab tests." (In-vitro diagnostics industry representative-Netherlands).

Whereas with regards the market in England, POCTs in general were seen as "a tough sell still" and whether there was demand for it in primary care was perceived "debatable" (In-vitro diagnostics industry representative-England).

Demand-side value

There is strong evidence that the introduction of CRP POCTs can reduce antibiotic use. This includes two randomized controlled trials (RCT) conducted in the Netherlands[35,36] and one conducted in five countries (including the Netherlands and England).[37] A before-and-after evaluation based on routine data collected from GP practices also found that the use of antibiotics decreased after the introduction of the tests.[38] However a long-term impact analysis of the multi-country RCT showed that the effect of the intervention did not last at 12 months of follow up.[39] With regards cost-effectiveness, studies also suggest that the use of CRP POCTs is cost-effective in the pathway of care for adults with pneumonia in both countries.[34,40,41] Cost-effectiveness of using the tests in children in primary care has not yet been examined.

As described later in section 5.5.3.6, in the Netherlands, CRP POCTs can be partially reimbursed under a fee-for service arrangement, i.e., a payment that is made retrospectively to GP practices for each use of CRP POCTs. In England, GP practices would need to bear the cost of using the tests, as there is currently no specific reimbursement scheme. From the interviews in this study, all of GPs in the Netherlands said that they found the tests very useful and none of them knew of other GPs who did not use them. Some said that although initially they were not particularly interested in the tests, this changed rapidly:

> "We had it and, as soon as we use it, we didn't want to give it back." (GP2-Netherlands).

In England, all of the interviewees mentioned a reluctance to bear the cost of using the tests. As with their counterparts in Netherlands, all of the GPs who had experience of using the tests in pilot studies said they found them useful, but recognized that their views were not always shared by others:

> "The other doctors are not at all convinced and so I think we never really got into a culture of using them a lot except for me" (GP1-England).

In both countries CRP POCTs were commonly said to help the decision to prescribe antibiotics, resulting in a perceived reduction in antibiotic use although one interviewee from the Netherlands expressed that this effect might not last, based on the long-term impact

analysis of the multi-country trial referred to above.[39] None of the interviewees were aware of whether the tests were considered cost-effective.

CRP POCTs were also perceived as helping to avoid sending patients to distant laboratories, a major difficulty expressed by most respondents from both countries. Another advantage of CRP POCTs for GPs in both countries was that it supported decisions and improved communication with patients, including with children:

"If I can't convince them (that antibiotics are not needed) myself I do it with the test" (GP2-Netherlands).

"They (children) loved having the test done and they wanted to know about it, and it was a chance to say most infections are viral and this shows you don't need antibiotics" (GP1-England).

Most GPs in both countries thought that CRP POCTs were not useful to inform decisions as to whether to refer a patient to hospital or not. However, a few GPs disagreed and did think they helped with this decision:

"If that (the need to refer) is really the case then you should already be able to see if the patient is really ill, and I don't think that the CRP, should make any difference in that" (GP3-Netherlands)

"It's more than just "I'll prescribe some antibiotics", it also helps to decide whether someone should be admitted to hospital" (GP3- England).

There were mixed views in both countries about the utility of using the tests in children, some expressing uncertainty about their added value, whilst others being more positive:

"There are lots and lots of kids we see with high fever, no diagnostic, no pointers to anything serious – it's a very common situation, and in that situation point-of-care testing would be very helpful" (GP1-England).

None of the interviewees were aware of whether the tests were considered cost-effective despite there being several studies as mentioned above.

Patients were not interviewed as part of this study. However, from the perspective of the GPs, some of them in the Netherlands reported that some patients wanted the tests to be used, particularly when they disagreed with the GP's decision or when they sought reassurance. In England, GPs reported mixed reactions with some patients liking the tests as it suggested to them that they were being taken seriously, whilst others being more mistrustful:

"It's almost like they go to hospital, and they turn up in Accident & Emergency" (GP2-England);: "some patients go: "I don't trust your machine doctor"" (GP3-England).

For GPs from practices where CRP POCTs were unavailable in England, there was a perception that if they were made available there would be demand for their use, which may not necessarily be a good thing:

"It would increase demand and then you risk that any child with an upper respiratory tract infection will cost you four pounds" (GP4-England).

5.5.3.4. The adopters (healthcare providers and patients)

Changes in staff roles, practices, and identities of healthcare providers

In this study the staff are GPs and practice nurses or assistants. In both countries, the implementation of CRP POCTs was not perceived to have changed their identities or practices, with the GPs responsible for seeing the patient and ordering the test, and the test then usually being performed by nurses or assistants. GPs saw the patient a second time only if the results were out of the normal range. This care pathway was like other pathways including the use of urine dipsticks or electrocardiograms and was perceived as "the normal work" (GP5-Netherlands). Having to see the patient a second time was perceived by all GPs in the Netherlands as acceptable. This perception seemed to contribute to the adoption of the tests by all interviewed GPs in the Netherlands.

By contrast, in England, GPs had more mixed views. Some thought the disruption was acceptable, while others thought using CRP POCTs extended the consultation time because they had to provide more information to patients and any increase in consultation time, even marginal and/or seeing the patient again was perceived as difficult:

"We had to tell them what is CRP, what does it mean, why does it mean that they don't need antibiotics, and what is the difference between a virus and a bacteria. It actually added more layers, layers of communication" (GP3-England).

"(Doctors and nurses...don't want to be messing around with three minutes, they are busy, very, very busy" (POC test implementor-England).

With regard to using the tests in children, in the Netherlands some GPs never used them in children while some did, but much less frequently than in adults. In England only one GP used CRP POCTs in children but also less frequently than in adults. In both countries, the reasons given included concerns about their accuracy and the absence of any reference to their use in children in guidelines.

Some GPs in England also found that finger pricking in children was invasive, and causing pain was perceived as undesirable.

Perceived acceptability by patients

All GPs in the two countries expected and reported that patients, including children, accepted the tests, if the GP decided to use it.

5.5.3.5. The organisations

In this study "organisations "refers to GP practices. In both countries GP practices are businesses that are run by GPs.[42,43] Their role in the care pathways for febrile children in the two countries is similar: they are the recommended first point of care and act as gatekeepers of other health services. However, some parents present directly to emergency departments, call an ambulance, or ask for advice from a pharmacist.[19,42,44,45] There are a few more options in England, such as telephone and online triage services and urgent treatment centres that can be accessed without appointments (Figures 29 and 30).[42,46,47]

Capacity to innovate

Most participants in both countries reported that the willingness and leadership to implement innovations varied across workplaces; some practices being keen to take-up innovations with others were perceived as being conservative and reluctant to try new things. As independent businesses, GP practices are free to decide whether they want to adopt diagnostics in both countries. However, the GPs interviewed in England expressed that their capacity to adopt CRP POCTs was limited by their heavy workloads, which made training and integrating new ways of working difficult, and because of the lack of financial support (see below).

Readiness for the implementation of CRP POCTs

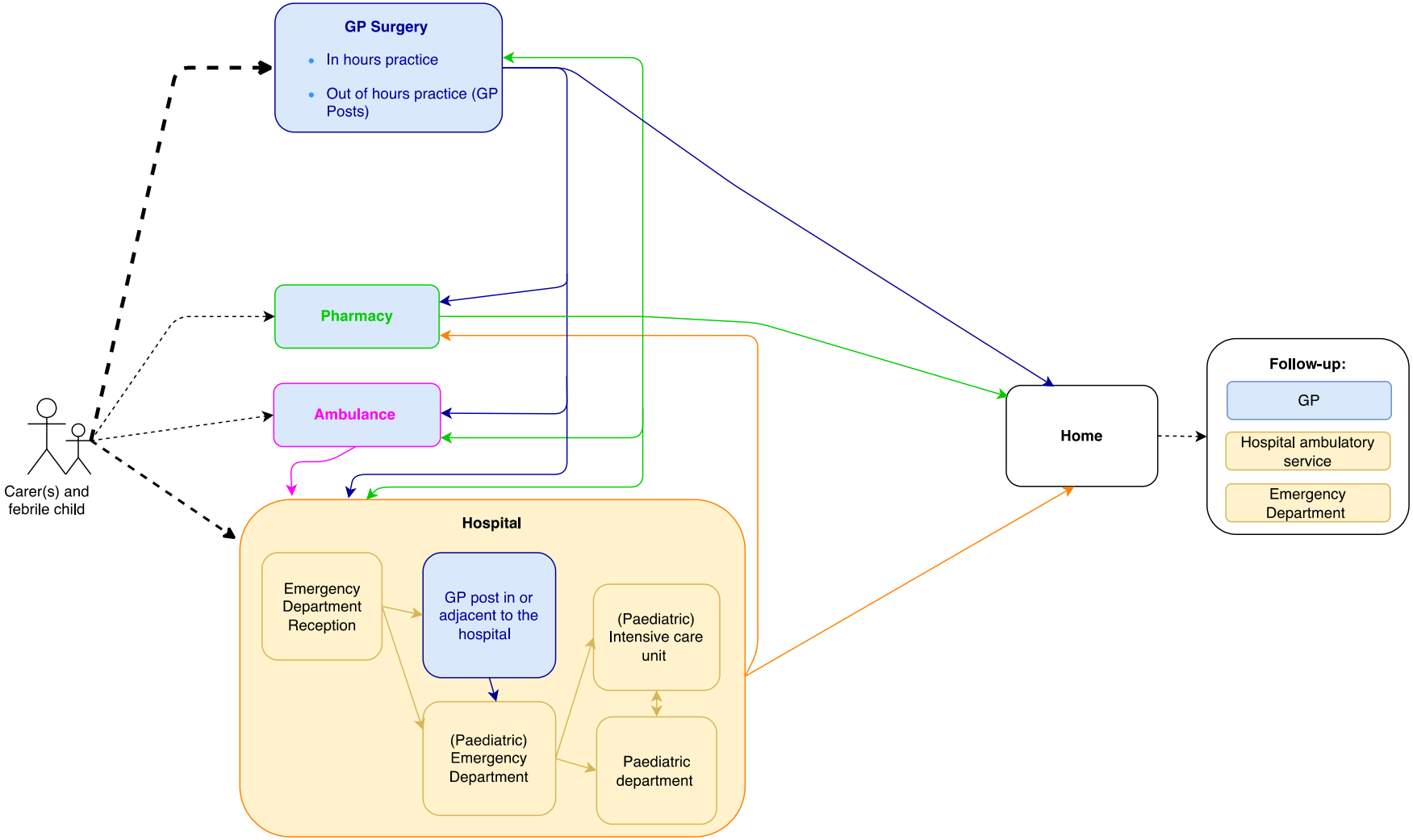
In the Netherlands, both hospital laboratories and primary care laboratories play an important role in implementing the tests in GP practices and in ensuring the tests are used in line with regulatory standards (see section 5.5.3.6),[48] as per the recommendations of the Dutch College of General Practitioners (NHG), the Dutch Association for Clinical Chemistry and Laboratory Medicine (NVKC), the Dutch Society for Medical Microbiology (NVMM), and the Laboratories Physicians Collaboration Netherlands (SAN).[49]

The existing operational support of laboratories to GP practices is likely to contribute to the readiness to implement CRP POCTs. In this study two of the three GP practices reported already having contracts with hospital laboratories that supported the implementation of other diagnostics prior to the introduction of CRP POCTs.

In England, there are very few primary care laboratories[50] and the role of hospital laboratories in providing support for the implementation of diagnostic tests in GP practices is limited. In this study participants mentioned that GP practices were not ready to implement CRP POCTs at scale and in a sustainable way, and that in part this was because of the lack of support from hospital laboratories:

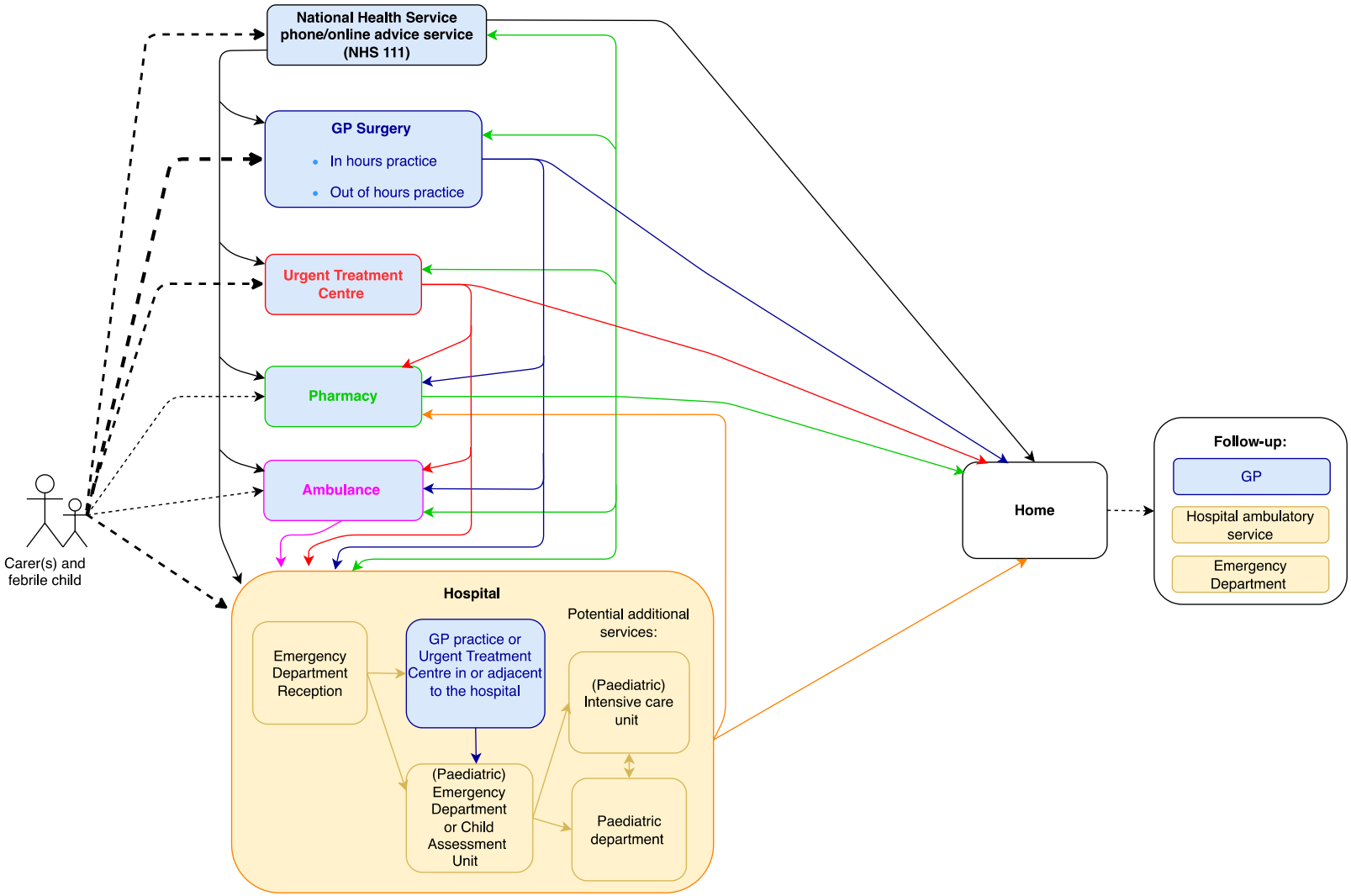
"They are busy enough inside (the hospital), if they want to come to see five practices within 20 miles, one person in a car driving out, whereas they got hundreds of machines in the lab, so they don't want to spend time travelling" (POCTs implementor-England).

Figure 29. GP practices in the care pathways for febrile children in the Netherlands



GP: General Practitioner

Figure 30. GP practices in the care pathways for febrile children in the England



GP: General practitioner

Integration (or the lack of within the health service) is an important factor in the adoption of CRP POCTs in GP practices and is explored in Section 5.5.3.6.

Funding decision

In the Netherlands, GP practices are financed by health insurance companies. These companies are mainly funded by the premiums received from the insured population (i.e., all residents, as being covered by health insurance is mandatory in the Netherlands).[42] The funding that GP practices receive consists of a combination of capitation, fee-for-consultations, bundled payments for integrated multidisciplinary care for chronic conditions, and pay-for-performance focused on accessibility and referral patterns.[51] In addition, few fee-for-service schemes exist, including a scheme that partially reimburses the use of CRP POCTs. As mentioned earlier, only the consumables to operate each test are reimbursed. The analyser must be purchased without reimbursement by the primary care or hospital laboratory that supports and implements the test in the GP practices as a capital investment.

In England, GP practices are funded by clinical commissioning groups (CCGs). CCGs are groups of general practices that commission health services for the population of their area. CCGs receive their funding from the national health service (NHS England) and allocate funds to each GP practice. The amount of funding received by GP practice is made up of a combination of capitation, pay-for-performance, fee-for-service, and additional funding for the maintenance of premises and seniority primes.[43,52,53] There are no pay-for -performance or fee-for-service schemes that fund the use of CRP POCTs, which means that GP practices need to pay for the full cost of using the tests from their budget.

Work needed to implement change

The implementation of CRP POCTs was seen as easy and straightforward by GPs in the Netherlands and for some GPs, the absence of CRP POCTs was actually more problematic than its implementation, suggesting that test is highly normalised:

> "We only had to make room for the machine. And our assistants got some guidance of how they had to do the test" (GP5-Netherlands).

"Sometimes it's broken, then we don't have one…That's the problem. That's basically it." (GP-5 Netherlands).

By contrast, in England, implementation was perceived as difficult. All the interviewed GPs mention that their practice would not want to pay for the tests from their budget. They would need to obtain funding form charities or convince the CCGs to allocate additional funding and then set up an agreement with a local hospital or directly with a diagnostic test company for technical support. All of this was perceived as very difficult:

> "Why should they (the CCG) invest this amount of money in a CRP project. So, I must say the fight to get mine was quite intense and I had to be very persistent" (POC tests implementor-England).

This was mainly caused by the funding constraints that CCG face (see section 5.5.3.6). Because of this, GP practices had to conduct pilot studies to convince CCGs of the clinical and cost-effectiveness of CRP POCTs use in the local care pathways. This led to the proliferation of pilot studies: In 2017, there were 34 pilot studies across the UK involving the use of CRP POCTs in primary care.[54]

5.5.3.6. The wider system

Policy context

Policies pertaining to antimicrobial resistance (AMR) were examined because the use of rapid diagnostic tests has been advocated as a means to reduce antibiotic use. The Dutch AMR policy recommends the use of new diagnostics to contain AMR but does not specifically mention POCTs.[55] Despite this, the implementation of CRP POCTs is one of the main antimicrobial stewardship measures in primary care.[38] The already low rate of antibiotic prescription in primary care decreased by 14% since 2011,[56] and the use of CRP POCTs has probably contributed to this decrease. In England, the UK AMR policy supports the use of POCTs generally but do not specifically mention CRP.[57] CCGs usually choose other antibiotic stewardship measures that have no or little additional costs over diagnostics (such as setting antibiotic prescription targets, or benchmarking of the use of antibiotics across GP practices and CCGs). The prescription of antibiotics decreased by 16% in primary care in the UK

between 2014 and 2019,[56] and some in England stressed that this was achieved because of these alternative antimicrobial stewardship (AMS) interventions.[58]

We also examined policies pertaining to the integration of health services, because the support of primary care and hospital laboratories to GP practices for the implementation of CRP POCTs was an important factor in the Netherlands. The concept of "transmural care" i.e., the integration within primary care and between primary and secondary care has been promoted to improve the quality of healthcare since the 1990s in the Netherlands. Since then, transmural care has become a common aspect of the organisation of health services, even though there is still room for improvement.[59] By contrast, integration within and between levels of healthcare is still in development in England, despite several attempts to integrate health services since the creation of the NHS.[60]

Regulatory context

All available CRP POC tests are CE marked in accordance with the European Union IVD Directive (98/79/EC).[25] CE marking is a process through which the manufacturer self-declares that the device conforms with EU regulatory standards.[61] This allowed manufacturers to commercialise their products legally in the EU, including the Netherlands and England (until December 2020 for the latter).

The relevant International Standards Organization (ISO) standards in both countries include ISO 15189 for the general laboratory activities of a laboratory supporting GP practices and ISO 22870 for the specific use of POCTs.[49,62]

Role of professional bodies

In the Netherlands, the Dutch Royal College of GPs played a key role in establishing the role of CRP POCTs in primary care. The use of these tests was recommended in clinical guidelines developed by the Dutch Royal College of GPs since 2011. This led the Dutch Healthcare Authority (NZA), an independent organisation that set tariffs for the reimbursement of health services, to include CRP POCTs (but not the analyser) in the list of medical devices that can be reimbursed to primary care services.[63] A tariff listed by the NZA mandates the reimbursement of the tests by health insurance companies:

"And we have to pay because by law, we have to ensure that they can get all the necessary care they need" (health insurance company representative-Netherlands).

Health insurers must reimburse health interventions that are included in a package called the Basic Package of Care.[43,64] The government decides the content of the Basic Package of Care,[43,65] based on the recommendations of the Zorg Instituut Nederland, another independent body in charge of health technology assessments (HTAs).[43,45,64,66] In theory, healthcare, including diagnostics, must be "normally provided by healthcare workers" and supported by "evidence of clinical and cost effectiveness" to be supported by the Zorg Instituut.[64,67] In practice, healthcare that is recommended in clinical guidelines is considered "normal" care and is almost automatically included in the Basic Package of Care. The Zorg Institute does not necessarily carry out prior HTAs, particularly if the innovation is not substantially expensive, which is the case of CRP POC tests.[42,65,67]

In England, although the 2014 NICE guideline on pneumonia recommended the use of CRP POCTs in the management of adults with suspected pneumonia,[34] these had limited impact in terms of their implementation in GP practices. The guidelines were produced with input from key stakeholders including the Royal College of GPs, however, NICE guidelines are only advisory and do not mandate the funding decisions of CCGs.

Financing issues

Both the UK and the Netherlands spend about 10% of GDP in healthcare.[18] However, health expenditure per capita in the UK is 16% lower than in the Netherlands. Containment of healthcare costs is a common issue across European countries but has been particularly important in the UK since 2010.[68,69] As a result, funding available to CCGs is relatively limited, and interview participants perceived that CCGs were very constrained financially and in deciding what to fund. This was perceived by some participants to give precedence to the treatment of non-communicable diseases, because of their greater contribution to the burden of diseases.[70]

Interorganisational networking

In both countries, there are regional support structures to help disseminating healthcare innovations, such as for example ROS Robust[71] in the Netherlands and the Academic Health Sciences Network (AHSNs) in England.[72] Additionally, some participants in the Netherlands mentioned the important role that early Dutch adopter played in generating local clinical, cost-effectiveness, and broader evidence about the use of CRP POCTs. They proactively disseminated the evidence and engage with all actors involved in the key decisions and processes that lead to the adoption of diagnostics in primary care. There are also "champions" in England who promoted and continue to promote the implementation of the tests.[37,73-76] It is difficult to estimate whether the work and intensity of efforts of these early adopters was greater or different across the two countries. However, the overall context described in detail across this paper was, and still is, more favourable and more receptive to the engagement of these actors in the Netherlands.

5.5.3.7. Adaptation of the technology, its use, and the organisations over time

Scope of adaptation over time

CRP POCTs devices cannot be physically changed or adapted. However, a few GPs in both countries reported that their use had extended beyond the conditions that had been included in original guidelines (cough, diverticulitis or COPD in the Netherlands; pneumonia in England). In England, a few participants mentioned that this had a negative impact on the perceived value of the tests by CCGs. There were also explorations in England to shift the use of the test to pharmacies,[77] yet this has not so far led to its implementation in those settings.

Organisational resilience

The concept of "diagnostic stewardship" with regards CRP POCTs has been gaining attention in the Netherlands. In 2018 the Zorginstituut launched a consultation of experts to improve the management of respiratory infections in primary care. One area of concern was the use of CRP POCTs in children, which was reported to the Zorginstituut by primary care experts informing the consultation.[78] The consultation will provide its recommendations in 2023.

In England, several recent reviews commissioned by the department of health on AMR and on improving the diagnostic capacity of the NHS have advocated for more adoption of

POCTs.[49,79] CRP POCTs are cited as an example with potentialities, which suggest that these tests have not completely been ruled out, despite the current barriers to their implementation. Many participants felt that the only way to implement CRP POCTs at scale in England would be that it is mandated by NHS England with a specific funding scheme:

> "It's only, it's only when things are mandated that things will get, done, really done" (Clinical commissioning group member-England).

5.5.4. Discussion

5.5.4.1. Summary of principal findings

A more favourable and receptive macro level environment combined with the endeavour and engagement of early adopters led to the successful adoption of the tests in the Netherlands. In the two countries, early adopters of the tests advocated for their implementation through the generation of robust evidence and by engaging with all relevant stakeholders. Their work was essential in creating awareness about the tests and about the evidence supporting their use among the actors involved in the adoption of diagnostics in health services. This led to the inclusion of CRP POCTs in national clinical guidelines in both countries. In the Netherlands, this resulted in mandating that the cost of the tests be partially reimbursed, under the fee-for-service reimbursement mechanism. Moreover, the prevailing better integration of health services enabled operational support from primary care and hospital laboratories to GP practices for the implementation of the tests. In England, the guidelines were only advisory and did not result in any mandates in relation to the use of or the reimbursement for CRP POCTs. Moreover, funding constraints and the resulting prioritization of less expensive antimicrobial stewardship interventions, the lack of integration across health services, the lack of operational support to GP practices and the resulting perception that the introduction of CRP POCTs would be a source of additional expenses and workload have all contributed to CRP POCTs not being adopted in England.

With regards the use of CRP POC tests in children with fever in primary care in the Netherlands and in England, this was often seen as a by-product of the test being made available for adult patients. In both countries, the tests are rarely used in children. This is

mainly because of concerns about the accuracy of the tests in children, the lack of guidelines specific for this age-group, and the perceived invasiveness of finger pricking in children.

5.5.4.2. Comparison with other literature

Other studies have investigated some of the different facilitators and barriers to the availability and use of POC tests in primary care presented in this paper.

We found that CRP POCTs were valuable for GPs for various reasons, with no distinctive pattern per country. Another study exploring the value of POCTs for GPs across European countries found that there was a variety of positive and negative views, and that these were shared across countries.[80] Better targeting of antibiotic use and supporting decisions and communication with patients were among the most cited values, which is in keeping with our findings.

We found that the interplay between early adopters and the overall context contributed to the adoption of the tests. In a study exploring the facilitators and barriers to the adoption of CRP POCTs in Northern European countries, Huddy and colleagues found that the work of early adopters was essential in facilitating the adoption of the tests because the early adopters acted in a favourable environment that encouraged POC technology and the reduction of antibiotic prescription. This in turn allowed the development of reimbursement schemes that supported large-scale adoption,[14] and is line with our study. A recent health technology assessment of CRP POCTs found that of 11 European countries that implemented CRP POCTs in primary care, a reimbursement scheme was available in seven countries (not data was available for the remaining four countries),[25] which suggest that reimbursement schemes contribute to the adoption of the test, which is in keeping with our findings.

Funding constraints in England was one of the major barriers to the implementation of CRP POCTs in our study. An independent review about the introduction of innovations in the NHS found that funding restrictions was limiting the adoption of innovations.[81] The most recent UK National Action Plan against AMR suggests that this was particularly true for diagnostics and that “if a new promising diagnostic came out tomorrow, the NHS is not equipped to get it into front-line use quickly”.[82]

Our study found that the tests were reportedly used less in children than in adults. Schot and colleagues in a qualitative study with GPs in the Netherlands also found that GPs use substantially less CRP POCTs in children because of concerns regarding the lack of accuracy and the invasiveness of the tests.[83]

5.5.4.3. Strengths and limitations

To the best of our knowledge, this is the first study to use the NASSS framework to compare the adoption of a healthcare innovation in two countries. Using the framework allowed us to conduct an in-depth, comprehensive, and consistent comparative health systems analysis. We conducted a document analysis in combination with interviews of a wide range of stakeholders in the two countries which allowed us to triangulate most of the findings presented in this article. Moreover, most studies on the adoption of POCTs focus on the adoption of the tests in adult patients; this is one of the few studies exploring the adoption of POCTs for the management of childhood infections. Our findings should be interpreted in light of some limitations, such as the small sample size for the different subgroups of stakeholders, the fact that we couldn't interview children and their carers, and the possibility that the background and experience of using POCTs by some of the authors may have created bias in the interpretation of data, despite the best attempts to limit this. Moreover, it is important to bear in mind that the qualitative data obtained from the interviews are the perceptions of participants and are not necessarily factual data.

5.5.4.4. Implications for organisations implementing POCTs and future research

This study shows that an in-depth analysis is needed to understand the reasons for the variability in the adoption of diagnostic tests in different countries. The NASSS framework is very useful in this regard.

There is evidence that the use of CRP POCTs can reduce antibiotic use in primary care. As noted earlier, the NHS in England achieved a 16% reduction in antibiotic prescriptions through alternative antimicrobial stewardship measures. This is encouraging, but this rate might be reduced even further if those measures are complemented by the implementation of technologies such as CRP POCTs. However, organizations considering the implementation

of POCTs in primary care should carefully consider how the implementation of the tests realistically fits into the wider national context.

Most participants questioned the accuracy and effectiveness of CRP POCTs for the management of febrile children in primary care. Additional research is needed to address these concerns and it may well be that newer and better tests could be transformative. Additional comparative analyses in other settings (i.e., hospitals) and countries and with other POCTs would also be useful to provide additional insights for the implementation of current and future POCTs.

5.5.5. Conclusion

A more favourable and receptive macro level environment including the influence of clinical guidelines, the funding environment, and the operational support from laboratory services to GP practices, combined with the endeavour and engagement of early adopters have led to the widespread adoption of the tests in the Netherlands. In both countries CRP POCTs, when available, are used much less frequently in children than in adults. This sis mainly because of concerns about their accuracy and the invasiveness of blood testing. These are important factors to consider for any organisations or individuals involved in the development and implementation of POCTs.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the London School of Hygiene & Tropical Medicine Ethics Committee (Ref:15040-15088). All methods were performed in accordance with the relevant guidelines and regulations of the London School of Hygiene & Tropical Medicine. All participants gave written informed consent to participate.

Consent for publication

No applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the London School of Hygiene and Tropical Medicine Compass data repository (https://datacompass.lshtm.ac.uk).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Juan Emmanuel Dewez (JED) and Shunmay Yeung (SY) conceived the study. JED and SY developed the initial study materials. Ruud G Nijman (RGN), Rebecca Lynch (RL), Ronald de Groot (RdG), Michiel van der Flier (MvdF), Ria Philipsen RP), contributed to the refinement of the study design. RdG, MvdF, and RP identified the initial stakeholders in the Netherlands. JED identified stakeholders in England. JED conducted all the interviews, SY participated to one interview. JED conducted the thematic analysis with cross verification from EF, and inputs from all co-authors. Harriet Vreugdenhil (HV) contributed to the interpretation of the results and their relevance to the Dutch primary care context. JED drafted this manuscript which was reviewed and edited by all co-authors.

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RL	BA, MSC, PhD	Researcher	Female	Medical anthropology
RdG	MD, PhD	Researcher	Male	Paediatrics, infectious diseases
MvdF	MD, PhD	Clinician-scientist	Male	Paediatrics, infectious diseases, translational research
RP	BSc	Researcher	Female	Cell biology and histology
HV	MD, PhD	Academic GP	Female	General practice
SE	MA, MSC, DrPH	Researcher	Female	Public health, health systems research
SY	MD, PhD	Researcher	Female	Paediatrics, infectious and tropical diseases, health economics, qualitative methods

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5.5.6. References

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5.6. Supplementary materials

Supplementary materials 1. Topic Guide (General Practitioners): Adoption of C-reactive protein rapid tests in primary care

Participant ID Number: Gender: Male / Female Country:

Introduction:

- Overview and purpose of study
- Present who is involved in the research
- Aims of interview and expected duration
- Explain why participant has been selected

- What will happen to the results of this study
- Solicit questions
- Go through consent form with participant

Warm-up and general information:

For how long have you been working as a GP? What is your role in the practice? What is the population affiliated to the practice? • Adults: • Children: Which rapid POCTs are available? How many devices are available? Distance to closest external lab? What samples are sent there? What is the distance to closest hospital?

Topics	Questions
1. Current practice	A 60-year-old lady that you haven't met before comes to your practice. She had had fever for 2-3 days (39). She is coughing a bit. She feels tired and has lost appetite. She hasn't been in contact with sick people. She has no major health antecedents. She appears a bit tired. Temperature 38.1, HR : 82/ min, RR 21/min, somewhat labored.

	Auscultation reveals few rhonchi and few late inspiratory crackles on the right side. The remainder of the lung fields is clear. The rest of the examination is normal • How would you manage this patient? • Would you use diagnostic tests? • Which tests? • And why? Now imagine that the patient is a 10-year-old boy. Same story Same physical examination but with HR 120 and RR 26 • How would you manage this child? • What are challenges, if any when seeing a child with acute fever? • Would you use diagnostic tests? • Which tests? • And why?

2. The technology and its value	• Have you used CRP POCT?
	  • If yes in which circumstances?
	  • What were the advantages/disadvantages of using CRP POCT?
	  ▪ For you?
	  ▪ For the GP practice?
	
	  • Have you used them in children?
	  ▪ If yes, what were the advantages/disadvantages of using CRP POCT in children?
	  ▪ If no, why?
	  • How did patients/children perceive the use of CRP POCT?

	• If no, why? • If because tests are not available, let's imagine the test are made available. • In which circumstances would you use the tests? • What would be the advantages/disadvantages of using CRP POCT? ▪ For you? ▪ For the GP practice? • Would you use them in children? ▪ What would be the advantages/disadvantages of using CRP POCT in children? • How would patients/children perceive the use of CRP POCT?
3. The adopters and the impact of CRP POCTs	• What changes, if any, did the use of CRP POCT brought/would bring to: o the way you work? o Your role in the practice? • Was the test accepted/ would the test be accepted by patients/parents/children? • Why yes/no?
4. The GP practice	• How innovative in general is your GP practice? • Can you tell me about an innovation that was introduced in your practice? What happened? • How ready was/is your practice for the introduction of CRP POCT?

	• What problems did you encounter/would you encounter in the implementation of CRP POCT? • Who decided/would decide whether the test should be adopted? • What are the criteria to decide to adopt tests such as CRP POCT? • How are/would be the cost of using the test be covered? • What impact did/would the use of CRP POCTs have on the way your GP practice is organised? • What work was/would be needed in your practice to adopt the test once the decision to implement it is taken? • What were/could be the main challenges in this process?
5. The wider context	• Are you aware of the AMR policy of your country? • What impact does it have on your willingness to implement/use CRP POCT? • What impact does it have on your prescription of antibiotics? • Are there other policies that have an impact on the use of diagnostics/antibiotics? • What role, if any, did your professional association had /could have on the process of implementing tests such as CRP POCT? • How do you get to know about innovations? How is the knowledge about innovations disseminated across GP practices?
6. Adaptation over time	• Has the use of CRP POCT changed since you started using it? Why? • How do you think the use of the tests would evolve if you started using it? • What could change the availability and use of CRP POCTs in the future?

End of interview:

- Ask participant if he/she has any question
- Ask if there is another relevant person he/she would recommend interviewing
- Ask if there is any document/website he/she would recommend accessing

- Thank participant.

Supplementary materials 2. Identification of documents for the document review

1. Criteria for considering documents for this review

Documents were included if they pertained to the adoption of diagnostic tests in primary care services in the Netherlands and England. This included:

- Publications in medical and health systems journals
- Clinical guidelines
- Information for patients about the use of diagnostic tests in primary care services
- Reports and recommendations of organisations involved in the organisation, funding, regulation, delivery, or evaluation of primary care services, with a focus on the implementation of diagnostic tests
- Policies with an impact on the implementation of innovations in primary care services
- Proceedings of conferences on diagnostic tests

2. Search methods for identification of documents

Documents were identified through a multi-pronged approach consisting of:

- Searching databases:
    - Pubmed
    - Google
- Searching websites of organisations involved in the organisation, funding, regulation, delivery, or evaluation of primary care services in the Netherlands and England:
    - GP practices
    - Clinical commissioning groups (in England only)
    - Health insurance companies (in the Netherlands only)
    - Professional associations of GPs
    - Organisations developing clinical guidelines
    - Local, national, and European health authorities
    - Independent organisations advising these health authorities

    - Agencies in charge of regulating the provision of healthcare
    - Agencies setting tariffs for medical procedures and technology
    - Independent organisations conducting health technology assessments
    - Independent organisations assessing health systems
    - Independent organisations in charge of disseminating innovations in health services
    - the European, Dutch and English in-vitro diagnostics industry
- Asking relevant documents to the 21 interviewees
- Attending relevant meetings and conferences about the implementation of diagnostic tests in health services
- Searching reference lists of identified documents

The search of data bases and websites were based on the following domains of enquiry:

5. Adoption (i.e., availability and/or use) of diagnostic tests
6. Epidemiology of fever in children
7. Care pathways for febrile children
8. Clinical performance, clinical effectiveness, and cost effectiveness of using CRP POC tests in primary care services
9. Organisation of primary care
10. Funding of diagnostic tests in primary care
11. Regulation of the use of diagnostic tests in primary care
12. Policies pertaining to antimicrobial resistance, integration of health services, and dissemination of technologies in health services

The search was based on a combination of medical subheadings (MeSh), key words, and synonyms for each of the domains of enquiry. The combination of search terms varied and was adapted to ensure it was relevant to the content of each database and websites (e.g., search terms pertaining to funding of diagnostics were used only in websites of organisations involved in the funding of health services).

There were no language restrictions. The search was conducted between 2019 and 2022, and restricted to documents published after 2000.

Chapter 6: (Research Paper 3) The adoption of C-reactive protein rapid tests in hospitals in the Netherlands and England: a comparative health systems analysis

6.1. Introduction

This chapter addresses Objective 4 of the thesis and aims to provide an in-depth understanding of the factors that contribute to the different levels of availability and use of CRP POCTs in hospitals in the Netherlands and England.

This research paper was submitted to BMC Health Services Research in March 2022 and is currently under review. The manuscript and supplementary materials are presented in the following sections.

6.2. Cover sheet

The Research Paper Cover Sheet is enclosed in the following pages.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	210537	**Title**	Dr
First Name(s)	Juan Emmanuel		
Surname/Family Name	Dewez		
Thesis Title	The adoption of rapid diagnostic tests for the clinical management of acute childhood infections in European settings.		
Primary Supervisor	Professor Shunmay Yeung		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The manuscript was submitted to BMC Health Services Research in March 2022 and is currently being reviewed.
Please list the paper's authors in the intended authorship order:	Juan Emmanuel Dewez, Ruud G. Nijman, Elizabeth Fitchett, Edmond C. Li, Queena F. Luu, Rebecca Lynch, Marieke Emonts, Rebecca Lynch, Ronald de Groot, Michiel van der Flier, Ria Philipsen, Stefanie Ettelt, Shunmay Yeung.
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study with my primary supervisor. I developed the protocol and study materials, and obtained ethical approval, with inputs from my primary supervisor and the co-authors. I conducted the documentary review and all the qualitative interviews in the Netherlands (one interview was conducted with Shunmay Yeung, one interview with Ruud Nijman). I conducted 5/28 qualitative interviews in England and supervised MSc students who conducted the remaining 23/28 interviews. I managed and cleaned the data arising from the study. I conducted the thematic analysis with inputs from Elizabeth Fitchett at an early stage, and then from all co-authors. I drafted the manuscript which was reviewed and edited by all co-authors. I submitted the manuscript.

SECTION E

Student Signature	
Date	25 November 2022

Supervisor Signature	
Date	20th December, 2022

6.3. Abstract

Background

The adoption of C-reactive protein point-of-care tests (CRP POCTs) in hospitals varies across Europe. We aimed to understand the factors that contribute to the different levels of availability and use of CRP POCTs for the management of acute childhood infections in hospitals in two countries.

Methods

A comparative qualitative analysis was used to examine the implementation of CRP POCTs in the Netherlands and England where the availability of the tests in hospitals is estimated to be 18% and 5%, respectively. The study was informed by the non-adoption, abandonment, spread, scale-up and sustainability (NASSS) framework. The data were collected through document analysis and interviews with stakeholders. The documents were identified through a scoping literature review, a website search, and through communications with the stakeholders. The stakeholders were sampled purposively initially, and then by snowballing. The data were analysed thematically.

Results

Forty-one documents were identified through the search and 46 interviews were conducted. The higher adoption of CRP POCTs in hospitals in the Netherlands is mainly because most hospital-based healthcare workers in the Netherlands are familiar with CRP POCTs as the tests are widely used and trusted in primary care. Moreover, although diagnostics are funded through similar Diagnosis Related Group reimbursement mechanisms in both countries, the actual funding for each hospital is more constrained in England. Compared to primary care, CRP POCTs are adopted less often in hospitals because cheaper laboratory-based CRP tests are usually available in hospitals, and the use of fewer and cheaper diagnostics is encouraged. However, CRP POCTs can be useful in some hospitals in which the laboratory cannot provide CRP measures 24/7 or within a short timeframe, and/or in emergency departments where expediting patient care is important.

Conclusions

CRP POCTs are more widely available in hospitals in the Netherlands because of the greater familiarity of Dutch hospital-based healthcare workers with the tests and because there are more funding constraints in England. However, most hospitals in the Netherlands and England have not adopted CRP POCTs because the alternative CRP measurements offered by the hospital laboratory are available in a only few hours and at a lower cost.

Key Words

Comparative health systems analysis, NASSS framework, C-reactive protein, point-of-care tests, the Netherlands, England, acute childhood infections, hospital care.

6.4. Manuscript

6.4.1. Background

Fever is a common reason for children to present to hospitals.[1,2] Most febrile children have self-limiting infections but differentiating the few febrile children with severe bacterial infections from those with self-limiting illness is difficult because the clinical features of infections in children are often non-specific.[3] Consequently, febrile children may be prescribed unnecessary antibiotics, subjected to invasive tests, and admitted for monitoring whilst awaiting microbiology results.[4] This causes pain, distress, and inconvenience, and may contribute to antimicrobial resistance (AMR).[5]

Point-of-care tests (POCTs) have been widely advocated.[6] They can be performed easily in the consultation room and provide rapid results. Using POCTs may reduce hospital admissions and optimise antibiotics and resource use.[7]

There are a number of POCTs that can be used in the clinical management of acute infections in children, although their impact varies.[8] These include urine dipsticks to diagnose urinary tract infections, rapid throat swabs to identify Group A Streptococcal infections, and C-reactive protein (CRP) POCTs performed on blood from a finger prick to differentiate bacterial from viral infections.[9] CRP is one of the most used biomarkers in the management of febrile children, but there are substantial ongoing efforts to develop new blood tests to determine the cause of fever with more precision.[10,11]

The availability and use of CRP POCTs seems to vary across Europe.[12] Understanding the reasons for this variation is important to inform the effective implementation of current and future POCTs, but this information is currently lacking.

The aim of this study was to generate an in-depth understanding of the factors that contribute to different levels of availability and use of CRP POCTs in hospitals in two European countries.

6.4.2. Methods

A comparative qualitative analysis based on two country case studies of the implementation of CRP POCTs was conducted. Qualitative methods were used because they are best suited to study phenomena such as the introduction of diagnostics in hospitals which is multifaceted and involves multiple actors and processes in a wider national context. The design of the study was informed by the non-adoption, abandonment, spread, scale-up and sustainability of healthcare technologies (NASSS) framework.[13] The NASSS framework was developed to identify factors that contribute to the adoption of innovations in healthcare services by assessing the complexity of seven domains: (1) the condition or illness; (2) the technology; (3) the value of the innovation for developers and users; (4) the adopters and whether the innovation implied a change in their identity and practices; (5) the organisations where the innovation is implemented, their readiness for this innovation, how the innovation changes the organisations' routines, and the work needed to adopt, fund, and normalise the innovation; (6) the wider context including the policy and regulatory contexts, the role of professional bodies and interorganisational networking; and (7) the adaptation of the innovation, its use, and the organisations over time (Figure 21).

The countries were selected to allow a "more similar" type of comparison,[14] i.e., the countries were different for the outcome of interest (availability of CRP POCTs in hospitals) but were similar in other aspects such as the care pathways for acute fever in children and the role of hospitals in this care pathways, the source of hospital funding, and the share of the country wealth that is invested in healthcare. An additional criterion was that there was an existing partnership between the research team and local researchers to ensure operational support. The selected countries were the Netherlands and England because in a previous survey we estimated that CRP POCTs are available in hospitals in 18% versus 5%, respectively (unpublished data, submitted for publication); the care pathway for acute fever in children is similar with general practitioners (GPs) being the recommended first point of care before hospitals; most (~80%) of health expenditure is covered by public sector sources in both countries (mainly from compulsory social health insurance in the Netherlands, and from general taxation in England);[15] and both countries invest approximately 10 % of gross domestic product on healthcare.[16]

Data were collected through an iterative process combining the analysis of documents and interviews with stakeholders. The document analysis sought to initially explore the wider health systems of the countries and to inform the identification of relevant stakeholders and

the development of topic guides (supplementary material). This was followed by interviews with stakeholders and additional document analyses. The iterative combination of these two methods allowed triangulation of data for two purposes: (1) to cross-validate findings and (2) to extend the understanding of findings.

Documents in English and Dutch were included if they pertained to the adoption of CRP POCTs in the two countries and were published after 2000. Documents included peer-reviewed publications, clinical guidelines, reports from healthcare organisations, health systems reviews, and policies. Documents were identified through a three-pronged approach. A scoping review of the literature was conducted by JED by searching Pubmed and Google on the following topics: epidemiology of febrile children; the clinical performance, clinical effectiveness, and cost effectiveness of CRP POCTs; the adoption of the test in the two countries; and the main characteristics of the countries' health systems. This was followed by an extensive search of the websites of relevant healthcare organisations (including clinical commissioning groups; professional associations of clinicians and industry; clinical guidelines development bodies; local, national, and European health authorities; independent bodies advising these authorities; independent bodies assessing healthcare interventions; health insurance companies; and the in vitro diagnostics industry). Finally, documents were also obtained through interviewees' recommendations and through attendance of relevant seminars and conferences.

Stakeholders were selected based on their expert knowledge of at least one domain of the NASSS framework pertaining to the adoption of CRP POCTs in hospitals in the included countries. We also ensured that we had at least one representative of the three level of health systems: micro (stakeholders who used/could use CRP POCT), meso (stakeholders directly involved in the implementation of diagnostics in hospitals) and macro (stakeholders involved in the wider national context).

Initial interviewees were sampled purposively. This was followed by snowball sampling to identify additional stakeholders that could provide insights on domains of the NASSS framework not covered in initial interviews. In the Netherlands, the initial interviewees were based in Nijmegen because members of the research team (RD, MVF, RP) were based there. Further stakeholders were based in Eindhoven and Leusden. RD, MVF, RP identified potential initial participants based on the inclusion criteria and contacted them (by email or telephone)

to ascertain their interest in being interviewed. Those who agreed, were followed-up by JED who provided a participant information sheet, obtained written informed consent, and arranged the interview date. In England, interviewees worked in Newcastle and London. Paediatricians and nurses were interviewed as part of a related project led by JED and SY aiming to explore the views of clinicians about using POCTs in general (not only CRP POCTs) in children.[17] The other stakeholders were identified through searching authors of medical articles on the use of CRP POCTs in England, by attending conferences about the adoption of diagnostics in the National Health Service (NHS) and by snowballing. JED conducted all the interviews in the Netherlands and the interviews in England with stakeholders other than paediatricians and nurses. Paediatricians and nurses in England were interviewed by EL and QL. SY participated in two interviews, and RGN participated in one interview in the Netherlands. The interviewers did not know participants beforehand. Face-to-face audio recorded interviews took place at the respondents' workplace between June 2018 and February 2020, and by videoconference between March 2020 and January 2022 because of restrictions due to the COVID-19 pandemic. Only the interviewers and the participants were present during the interview. All interview records were transcribed verbatim by a research assistant, EL, QL, or JED. Field notes were taken after each interview. One transcript was returned to a participant who requested this; no corrections were made. One participant was recontacted to clarify the information provided in the interviews. No repeat interviews were conducted.

The documents and interview transcripts were analysed thematically. The analysis was deductive based on the seven domains of the NASSS framework. JED extracted data from the interview transcripts and documents and collated them per NASSS domain using matrices in Excel, including alternative views, when available. EF independently assessed whether each extract was assigned to the most relevant NASSS domains. Discrepancies were resolved through discussion and consensus between JED and EF. Data from the two countries were analysed separately. A summary of each domain was produced and the summaries of the two countries were then compared descriptively to highlight similarities and differences for each domain. All authors verified the consistency of each domain summary. Data saturation was considered reached when all domains of the NASSS framework were covered and each domain was clearly understood. Participants did not provide feedback on the findings.

6.4.3. Results

Forty-one documents including research publications, clinical guidelines, proceedings of workshops, health services assessments, health systems reviews, and policies were included in the analysis (Table 9).

A total of 46 stakeholders were interviewed. This included healthcare workers (nurses, paediatricians, and laboratory staff) from four hospitals (two hospitals in each country). CRP POCTs had been used in the emergency department (ED) of one of the hospitals in England as part of a pilot study. One hospital in the Netherlands was about to implement CRP POCTs in its ED and in the two remaining hospitals the tests were never used, nor were there plans to do so. Other stakeholders included representatives of a clinical commissioning group, a health insurance company, an interorganisational networking public body and the in vitro diagnostics industry (Table 10). Four successive industry representatives did not reply to the invitation in England. Interviews lasted 31-75 minutes.

The analysis identified similarities and differences in the seven NASSS domains between the two countries (Table 11) and are presented narratively below. In the narrative we intertwined data from the documents and the interviews pertaining to each domain of the NASS framework to synthesise the findings.

6.4.3.1. The condition (acute fever in children)

The burden of acute fever in children is similar in both countries. Studies estimated that acute fever is the main cause of consultation in hospitals' EDs, in around 15 % of children in the Netherlands,[1] and in around 14% in England.[2] Other studies estimated that 0.1-1% of children with acute fever presenting to EDs had severe infections such as septicaemia or meningitis in the Netherlands compared to 1-2.4% in England.[18,19]

Table 9. Documents included in the analysis about the adoption of CRP POCTs in hospitals

Author and country	Title	Type of document	NASSS domains
Van Ierland, 2011[1]	Self-referral and serious illness in children with fever.	Observational study aiming to compare febrile children referred by a general practitioner with those self-referred in the Netherlands.	Domain 1
Sands, 2011[2]	Medical problems presenting to paediatric emergency departments: 10 years on.	Observational study aiming to describe the common medical presenting problems of children attending a paediatric emergency department.	Domain 1
Nijman, 2013[18]	Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study.	Diagnostic test accuracy study of a predictive model for the assessment of the risks of serious bacterial infections in children with fever at the emergency department in the Netherlands and England.	Domain 1 and 7
Le Doare, 2014[19]	Very low rates of culture-confirmed invasive bacterial infections in a prospective 3-year population-based surveillance in Southwest London.	Observational study aiming to estimate the incidence, clinical characteristics, and risk factors for culture-confirmed invasive bacterial infections in England.	Domain 1
O'Brien, 2019[20]	CRP POCT to guide antibiotic prescribing in primary care settings for acute respiratory tract infections.	Health technology assessment of CRP POCT.	Domain 2
Van den Bruel, 2011[21]	Diagnostic value of laboratory tests in identifying serious infections in febrile children.	Systematic review of the diagnostic test accuracy of various biomarkers including CRP to predict serious bacterial infections.	Domain 2
NVK, 2013[22]	Bacterial meningitis.	Guidelines from the Dutch College of Paediatrics on meningitis.	Domain 2
NVKb, 2013[23]	Fever in secondary care in children aged 0-16 years.	Guidelines from the Dutch College of Paediatrics on fever.	Domain 2

NVK, 2021[24]	Sepsis in children.	Guidelines from the Dutch College of Paediatrics on sepsis in children.	Domain 2
NVK, 2017[25]	Prevention and treatment of early-onset neonatal infections.	Guidelines from the Dutch College of Paediatrics on sepsis in neonates.	Domain 2
NICE, 2010[26]	Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis, and management.	Guidelines from the National Institute for Health and Care Excellence on meningitis in children.	Domain 2
NICE, 2019[27]	Fever in under 5s: assessment and initial management.	Guidelines from the National Institute for Health and Care Excellence on fever in children < 5years.	Domain 2
NICE, 2021[28]	Neonatal infection: antibiotics for prevention and treatment.	Guidelines from the National Institute for Health and Care Excellence on neonatal infections.	Domain 2
NICE, 2007[29]	Urinary tract infection in under 16s: diagnosis and management.	Guidelines from the National Institute for Health and Care Excellence on urinary infections in children.	Domain 2
RCPCH, 2021[30]	COVID-19 - guidance for management of children admitted to hospital and for treatment of non-hospitalised children at risk of severe disease.	Guidelines from the British Royal College of Paediatrics and Child Health on COVID-19.	Domain 2
Oxford AHSN, 2017[31]	Unique point of care blood test speeds up clinical decision-making, improves quality of care and reduces costs.	Report of a pilot study to assess the effectiveness of CRP POCT use in children to reduce length of stay in EDs and costs of care in three hospitals.	Domain 3
Cylus, 2015[32]	United Kingdom health system review	In-depth review of the British health system.	Domain 5 and 6
Kroneman, 2016[33]	The Netherlands health system review.	In-depth review of the Dutch health system.	Domain 5 and 6
Maguire, 2011[34]	Which urgent care services do febrile children use and why?	Observational study aiming to explore how parents navigate urgent and emergency care services when their child <5 years old has a feverish illness	Domain 5

Mossialos, 2017[35]	International profiles of healthcare systems, 2016.	In-depth review of the Dutch health system.	Domain 5
Luppa, 2018[36]	Point-of-Care Testing Principles and Clinical Applications.	Multi-country evaluation of POC testing in hospitals.	Domain 5
BIVDA, 2016[37]	Point of care testing environment survey report.	Survey by a British in vitro diagnostics professional association about the readiness of NHS trusts to implement POCTs.	Domain 5
van Stijn, 2012[38]	Data Quality of the Dutch DBC Information System	MSc thesis assessing the data quality of the DBC information system within Dutch hospitals.	Domain 5
Busse, 2011[39]	Diagnosis related groups in Europe: moving towards transparency, efficiency, and quality in hospitals?	Review of European health financing schemes	Domain 5
Academy of Medical Sciences, 2021[40]	Building a sustainable UK diagnostics sector	Summary report of a FORUM workshop	Domain 5
Dutch government, 2015[41]	Tackling antimicrobial resistance, the Dutch one health approach.	Summary of the Dutch antibiotic resistance policy.	Domain 6
UK government, 2013[42]	UK 5-year antimicrobial resistance strategy 2013 to 2018.	British antimicrobial resistance plan.	Domain 6
Monitor, 2014[43]	Exploring international acute care models.	Multi-country analysis of acute service line models by Monitor, the regulator for health services in England.	Domain 6
NHS England, 2019[44]	Clinically led review of NHS access standards	Report from the NHS National Medical Director on NH standards.	Domain 6
Parkin, 2020[45]	NHS maximum waiting time standards	Briefing from the House of Commons on the NHS waiting time standards.	Domain 6
Carter, 2006[46]	Report of the Review of NHS Pathology Services in England	Independent review of NHS pathology services.	Domain 6

Royal College of pathologists, 2017[47]	Consolidation of pathology services: lessons learnt.	Report of accounts from members of the Royal College of Pathologists about their experience of consolidation of pathology services.	Domain 6
Satta, 2018[48]	Consolidation of pathology services in England: have savings been achieved?	Descriptive comparison of savings among consolidated and non-consolidated pathology services.	Domain 6
Jeurissen, 2021[49]	The market reform in Dutch health care.	In-depth review of the healthcare market reforms in the Netherlands.	Domain 6
Anderson, 2021[50]	Re-laying the foundations for an equitable and efficient health and care service after COVID-19	LSE-Lancet Commission on the future of the NHS.	Domain 6
OECD, 2020[51]	Health spending, 2020.	Report on health spending in countries member of the Organisation for Economic Cooperation and Development.	Domain 6
European Commission, 2021[52]	CE marking.	Information for the public about the European Union's single market standards.	Domain 6
ROS Robuust[53]	Robuust for healthy collaboration.	Information for the public about regional support to healthcare services collaboration in the Netherlands.	Domain 6
AHSN, 2021[54]	Academic Health Science Network: transforming lives through healthcare innovation.	Information for the public about regional support to dissemination of healthcare innovation in England.	Domain 6
de Vos-Kerkhof, 2015[55]	Impact of a clinical decision model for febrile children at risk for serious bacterial infections at the emergency department.	Clinical trial aiming to assess the impact of a clinical decision model for febrile children attending the emergency department in the Netherlands.	Domain 7
van de Maat, 2020[56]	Evaluation of a clinical decision rule to guide antibiotic prescription in children with suspected lower respiratory tract infection in The Netherlands.	Clinical trial aiming to assess the impact of a clinical decision model for children with lower respiratory infections attending the emergency department in the Netherlands.	Domain 7

Table 10. Characteristics of stakeholders

Stakeholders	Netherlands			England			Main health system level
	Non-hospital stakeholder	Hospital 1 (secondary hospital)	Hospital 2 (tertiary hospital)	Non-hospital stakeholder	Hospital 3 (tertiary hospital)	Hospital 4 (tertiary hospital)	
In vitro diagnostics industry representative	1			1			Macro
Health insurance company representative	1						
Clinical commissioning group member				1			
Reimbursement of healthcare expert	1						
Health services networking expert (AHSN)				1			
Head of laboratory department		1	2				Meso
POCT manager						1	
Head of emergency department		1			1		
Emergency department nurse		1	2		1	3	Micro
Emergency department doctor			1		3	2	
Paediatric infectious diseases doctor			1				
General paediatrician		1	1		2	1	
Paediatric trainee		1	1		6	6	
Emergency Department trainee		1					
Total	17			29			

AHSN: Academic Health Science Network

Participants in both countries felt that clinically differentiating severe infections from a viral infection is hard particularly in young infants. Most participants mentioned that, because of this, they prescribe antibiotics, use several diagnostic tests, and observe many children in hospital for several hours:

"We perform lots of tests that aren't really necessary" (paediatric infectious diseases doctor-Netherlands);

"We observe children cover the bases and to make sure that children are being treated and that nothing (severe) is missed" (nurse 2-England).

6.4.3.2. The technology

Material features

CRP POCTs were developed in Scandinavian countries.[20] There are 15 different commercially available CRP POCTs. Twelve are quantitative readers and three are semi-quantitative devices.[20] Only quantitative devices were considered because these are the types of devices that have been implemented in the two countries and that were the focus of the documents included in this study.

The tests measure CRP levels in whole blood. As only a small volume of blood is required, it can be obtained from a finger prick rather than venepuncture. Additional preparation, such as centrifugation is not required. The drop of blood is place on a cartridge which is plugged into a small mains-powered reader that provides results in around five minutes. In comparison, for CRP measured in the hospital laboratory, most participants reported that the turnaround time to obtain results was around one hour in the Netherlands, while it was around two to three hours in England.

A systematic review and meta-analysis found that CRP measured in a laboratory is one of the best biomarkers currently available to identify severe infections in children.[21] However, it can take up to 48 hours from the onset of infection before CRP peaks.[20] Because of this delay, most participants in both countries felt that low levels of CRP were not useful to exclude severe infections.

Table 11. Summary of differences in the NASSS domains that explain the difference in adoption of CRP POCTs in hospitals between the Netherlands and England

Domains	Summary of differences (Green: minor differences; amber: moderate differences; red: major differences)
1. The condition (acute fever in children)	• The burden of children with acute fever presenting to emergency departments, the perceived difficulty in differentiating mild illnesses from infections that warrant the use of other diagnostics and antimicrobials, and concerns about missing severe infections are similar in both countries.
2. The technology (CRP POCTs)	• The technology, and its supply model are similar in both countries. • Most participants in both countries thought that high levels of CRP were helpful in identifying potentially severe infections but had reservations about the accuracy of low levels of CRP in ruling them out.
	• Few participants in England thought that CRP POCTs were dependable diagnostic tests, while most participants in the Netherlands perceived that the devices were reliable; this was mainly because of the familiarity of Dutch interviewees with the tests which are widely used in primary care in their country.
	• Any healthcare worker in either country can be trained to operate CRP POCTs. • Most participants thought it was easier to obtain blood from finger pricking than venous sampling. • Several participants mentioned that the inclusion of CRP POCTs in clinical guidelines would influence the use of the tests. Several guidelines recommend the use of CRP in children with acute infections in both countries, but none specifically recommend the use of CRP POCTs.
3. The value of CRP POCTs for industry, users, and patients	• There is a trend in both countries towards the consolidation of pathology services, i.e., centralising laboratory activities in bigger hospitals. This was perceived in principle as a commercial opportunity for POCTs in both countries.
	• There was a variety of views regarding the value of CRP for healthcare workers with no specific pattern per country. Common values were that CRP supports clinical decisions (such as antibiotic prescription, the use of other diagnostics, and admitting the patient) and improve communication with parents or carers.
	• There were common perceptions about the value of CRP POCTs in both countries. The tests were valued because they helped accelerate the flow of patients in EDs and from the ED to other

	wards. CRP POCTs were also valued because they were perceived as less invasive.
	• In both countries, participants reported that reducing the length of stay in EDs could reduce costs and be beneficial for the hospitals as a whole. However, this depended on the local set up and was less valuable if the hospital laboratory was able to provide CRP in 1-2 hours. • Participants reported a variety of parental perceptions about diagnostics, ranging from not expecting diagnostics and not being familiar with CRP POCTs, to parents expecting tests, but not necessarily CRP POCTs.
4. The adopters	• The implementation of POCTs in hospitals changed the role and identity of laboratory personnel in both countries because they had to supervise the use of diagnostics by non-laboratory personnel outside of the laboratory. This created some initial resistance from laboratory personnel. • Doctors and nurses usually accept using CRP POCTs because this does not change their role or identity as they already use diagnostics and other POCTs in both countries. • Some participants reported or feared that introducing CRP POCTS could lead to an indiscriminate use of the tests in both countries. • In both countries, most participants reported that parents and carers usually accept the tests if healthcare workers decide to use them.
5. The organisations	• In both countries, hospitals are not the recommended first point of care for children with acute fever. Febrile children are expected to be seen by GPs first. • The vast majority of hospitals operate as not-for-profit organisations in both countries. • The leadership and willingness to adopt innovations varies across hospitals with no specific pattern per country.
	• In England the capacity to implement innovations was perceived as limited mainly due to funding constraints.
	• In both countries, hospital laboratories adapted to the increasing demand for POCTs by assigning personnel to manage POCTs. It is estimated that all hospitals in the Netherlands have a POCT team in place, while most hospitals in England are staffed with at least one POCT coordinator.
	• The funding of diagnostic tests use in hospitals is included in the case mix funding of the Diagnosis Related Group (DRG) reimbursement mechanism in both countries.
	• In both countries, implementors of POCTs have to conduct pilot studies to demonstrate the diagnostic accuracy, the clinical

	effectiveness, and the saving of costs made possible by the introduction of the tests in the hospital. This was perceived as resource intensive and difficult to achieve if the laboratory could provide CRP in few hours 24/7.
	• The clinical and cost effectiveness criteria could be very stringent in some hospitals in England because of the funding constraints they face.
	• The introduction of CRP POCTs was not perceived as disrupting the ED activities by participants who used the tests, nor expected to be disruptive by those who were planning to implement it.
	• In both countries, the implementation of CRP POCTs required substantial work to organise the training of healthcare workers, the development of local guidelines and the design of quality assurance mechanisms.
6. The wider context	• AMR policies in the Netherlands recommend the use of diagnostics to address AMR, but do not mention POCTs. In England, AMR policies recommended the use of POCTs but not CRP POCTs specifically.
	• There are no policies pertaining to the time spent by patients in EDs in the Netherlands, while in England it is expected that at least 95% of the patients leave the EDs within four hours, although the financial fines for not reaching this standard were abolished in 2016.
	• Policies promoting the consolidation of pathology services, have been implemented in both countries over the last decade. • CRP POCTs met regulatory criteria in both countries. • There are interorganisational networks in both countries that support the dissemination of innovations across hospitals.
	• There are funding constraints in both countries, but these are more pronounced in England where health expenditure per capita is 16% lower than in the Netherlands. This was perceived by several participants as a major barrier.
7. Adaptation of the technology over time	• Adapting the way that CRP POCTs are used in febrile children presenting to hospitals was explored by combining CRP POCTs results with clinical signs in a predictive model in both countries. The model accurately predicts the risk of severe infections, but when used in recent trials did not reduce length of stay nor antibiotic use.

CRP: C-reactive protein; ED: Emergency Department; POCT: point-of-care test; DRG: Disease related Group

In terms of the accuracy of POCTs devices to measure CRP, several studies showed that the devices were accurate and precise compared to the measurement of CRP in a laboratory.[20]

Despite this evidence, few participants in England thought that CRP POCTs were dependable diagnostic tests. By contrast, most participants in the Netherlands perceived that the devices were reliable, and this view was mainly because of the familiarity of Dutch interviewees with the tests, as the tests are widely used in primary care settings:

> "CRP POCTs are widely used in the General Practice population, so the machines are (already) validated quite properly"(head of emergency department-Netherlands).

Types of knowledge generated

Quantitative CRP POCTs provide a measure of blood CRP concentration in mg/L.

Knowledge and support to use the tests

Any healthcare professional in the Netherlands and England can be trained to operate the tests. Most participants in both countries thought that using CRP POCTs was easy and that getting a quick result was a major advantage:

"It is a lot easier in children than trying to get a venous blood sample", trainee 4-England).

Several participants mentioned that the inclusion of CRP POCTs in clinical guidelines would influence their use of the tests. In both countries, some guidelines for the management of infections recommend using CRP, but not specifically CRP POCTs. Guidelines from the Dutch Royal College of Paediatricians (NVK) recommend the use of CRP in the clinical management of meningitis,[22] fever,[23] sepsis in children,[24] and neonatal sepsis.[25] In England, the National Institute for Health and Care Excellence (NICE) guidelines for meningitis,[26] fever in children <5 years,[27] and neonatal infections[28] recommends the use of CRP in similar terms to the Dutch guidelines. The NICE guidelines for urinary tract infection[29] advise against using CRP alone to differentiate between pyelonephritis and cystitis in children. There is also a recent guideline from the Royal College of Paediatrics and Child Health that recommends the use of CRP to decide whether to initiate immunomodulatory therapy in children with COVID-19.[30]

Technology supply model

The devices do not need to be locally customized; they are a 'plug and play' technology. There are
several companies that produce CRP POCTs, several of them being multinational companies that supply the Netherlands and England.[20]

6.4.3.3. The value propositions

Supply-side value

Some participants reported that there was a trend towards reducing the volume of activities in smaller hospital laboratories and to centralize or consolidate these activities to main hospitals in both countries (see section 6.4.3.6). This led to the perception that the use of POCTs will increase in the future to cope with this change and it also suggests that this may increase the commercial value of POCTs in general:

> "There will be more and more point of care in the hospital wards" (in vitro diagnostics industry representative - Netherlands).

In the Netherlands, some participants felt that this trend facilitated the implementation of POCTs. By contrast, in England there was more diversity of views with few participants reporting that consolidation of pathology services promoted the implementation of POCTs, while an industry representative felt that the business case for POCTs has not "stacked up" yet and that the demand for POCTs is low. This suggests more uncertainty about the commercial value of POCTs in England:

> "Even though the diagnostics industry is in principle interested in investing in POCTs, there needs to be (more) demand" (in vitro diagnostics industry representative - England).

Demand-side value

There were mixed views regarding the value of CRP and CRP POCTs for healthcare workers, with no particular differences between the two countries.

Some participants thought that CRP can help clinical decision making, such as whether or not to prescribe antibiotics, use additional diagnostic tests and whether to admit or discharge patients, particularly in those with no clear focus of infection. CRP was also perceived by some participants as useful when communicating with parents or carers to reassure them and support decisions.

In terms of CRP POCTs, one participant reported that the tests allowed "decision making a lot quicker" (nurse 3-England), a value that was shared by most participants. Another commonly cited value was that finger pricking was less invasive than venous sampling. The need for only "a few drops of bloods" (paediatric infectious diseases doctor-Netherlands) was also valued by most participants. However, some participants mentioned that this did not apply to patients with multiple morbidities:

"(In complex cases) you would normally do the whole shebang (other diagnostics) rather than just do the screening test (CRP POCT)"; Trainee 12 – England).

Few paediatricians mentioned that with the use of POCTs, including CRP POCTs, laboratory sampling errors (labelling errors, or loss of samples) might be reduced, although other participants pointed out that these were rare events.

In terms of the value of CRP POCTs at the hospital-level, several participants mentioned that the use of CRP POCTs helped accelerating the flow of patients in the ED and between the ED and other services:

"It helps getting people through quickly" (head of emergency department-Netherlands).

This in turn freed capacity (rooms, beds, availability of healthcare workers) and was particularly important for smaller EDs which struggle to manage the volume of patients in busy periods of the year. Some participants in both countries also suggested that CRP POCTs could be particularly valuable in smaller hospitals that had scaled back laboratory activities or did not have an onsite laboratory out-of-hour. In those settings, allowing the ED personnel to use CRP POCTs might be cheaper than having, for example, a laboratory technician on call.

To the best of our knowledge, there were no cost-effectiveness evaluations of the use of CRP POCTs in hospitals in children. A cost-saving assessment of a pilot study in England found

that using CRP POCTs in children attending the ED resulted in a reduction in the length of stay in EDs and annual savings of more than £60,000 across three hospitals, mainly through the reduction of clinicians' workload.[31] However, the value of accelerating patient flow was thought to be context dependent. Most participants reported that their hospitals were able to provide CRP results from the laboratory in a few hours and some thought that the accuracy of results from the laboratory were more reliable. Because of this, several healthcare workers thought that the longer turnaround times for samples analysed in the hospital laboratory compared to the POCTs were acceptable.

In terms of the value of CRP POCTs for parents of febrile children, few participants reported that the expectations of parents varied:

"There is a massive variety of parental expectations" (trainee 4-England).

In both countries, parents are not usually familiar with CRP POCTs. Although it was reported that parents of children with multiple comorbidities and children referred by a GP tended to expect more diagnostics in general, this does not apply specifically to CRP POCTs.

6.4.3.4. The adopters (healthcare workers and patients)

In this study, healthcare workers were hospital nurses, paediatricians (including specialist trainees), and laboratory personnel. In both countries, the introduction of POCTs in hospitals changed the role of laboratory personnel, because they had to supervise the use of diagnostics outside of the laboratory:

"We take full responsibility (about the use of POCTs), including the training, the quality control… everything" (head of laboratory 1-Netherlands).

This generated some initial resistance towards POCTs as it increased the workload of laboratory staff.

In England, the implementation of CRP POCTs in a pilot study at one of the hospitals included in the study did not change nurses or doctors' roles or identity because they already used other POCTs. In the Netherlands, CRP POCTs were about to be introduced in one of the

hospitals, and the implementors expected that most staff would accept using the tests because of they already routinely use other POCTs, although other participants reported that there might be some resistance from more senior nurses who were reported to be less inclined to adopt innovations.

Some participants in both countries feared that introducing CRP POCTs would lead to healthcare workers overusing the tests:

"Before you know it, it would get out of hand maybe, and you need to do the test in every patient who comes with a runny nose" (paediatric infectious diseases doctor-Netherlands).

This happened in the hospital in England where the tests had been piloted and was one of the reasons for the test being abandoned after the pilot:

"It (CRP POCTs) did eventually become used indiscriminately which was a problem" (head of emergency department-England).

Acceptability by patients and carers

None of the participants in either country reported that parents and children refused POCTs, including CRP POCTs. One participant believed that this was because they trust the use of technology by healthcare workers:

"Parents put great faith in technology" (trainee 9-England).

6.4.3.5. The organisations

The organisations considered in this study were hospitals. In both countries, parents and other carers of children with acute infections are expected to initially seek medical care at GP practices, as GP are the gatekeepers of health services.[32,33] However, in both countries some patients do present directly to hospitals,[1,34] usually at the ED. Most hospitals operate as not-for-profit organizations in both countries.[35]

Capacity to innovate

There were mixed views in terms of the leadership and willingness to adopt innovations. In both countries, few participants reported that this varied across and within workplaces:

"It completely depended on the person (in charge)" (head of laboratory 1-Netherlands).

In terms of resources, resource constraints were commonly mentioned, but this was particularly the case in England where implementing innovations was perceived as difficult mainly due to funding constraints (see section 6.4.3.6).

Readiness for the implementation of CRP POCTs

Hospital laboratories in both countries have progressively assigned specific personnel to oversee the use of POCTs over the last decade to address the increasing demand for POCTs in general. In the Netherlands, a recent cross-country evaluation of quality assurance of POC testing estimated that most hospitals have a POCT team in place;[36] in England, a survey of NHS trusts found that this was the case in 70% of the surveyed hospitals.[37] This may have increased readiness to implement POCTs, although one participant in England reported that many hospitals actually have only one person in charge of POCTs (rather than a team) and suggested that this person was sometimes overwhelmed which might be a barrier to the implementation of POCTs.

Funding decision

The funding of diagnostic tests in hospitals is included in the case mix funding of the Diagnosis Related Group (DRG) reimbursement mechanism in both countries, called Diagnosis Treatment Combination system (DOT-DBC) in the Netherlands and Payment by Result in England.[32,32] In both countries, clinical cases are classified into groups which comprise cases that are clinically similar and are homogenous in terms of resource use (e.g., medical and surgical procedures, severity, length of stay). The sum of money that is reimbursed for providing care to each group, including the use of diagnostics, is set in advance by the Dutch Health Authority (NZA) in the Netherlands and by the Department of Health in England,[38,39] based on average costs of care for each clinical condition across all hospitals. Each group is assigned a code and hospitals bill the codes generated through their activity to the funder of hospital care. In the Netherlands funders are not-for-profit health

insurance companies, while in England they are clinical commissioning groups, which are public organisations funding primary and hospital care for the population of a geographical area. Under this system, hospitals receive a fixed sum of money per case, regardless of the number of diagnostic tests used. This incentivises hospitals to limit their expenses for each case to ensure they do not exceed the reimbursement they receive. This may discourage the use of CRP POCTs which are more expensive than CRP measured in the laboratory, except if using the tests reduces costs elsewhere by, for example, reducing length of stay. In both countries it is necessary to present a business case with the potential cost savings generated by introducing the tests in the hospital care pathways "to justify the costs of CRP POCTs" (general paediatrician 2-England). Moreover, pilot studies are required to demonstrate the diagnostic accuracy of POCTs compared to the laboratory equivalent. In England, some participants reported that the level of evidence needed to justify the adoption of new diagnostics varied across hospitals and was sometimes very stringent. A recent workshop by the Academy of Medical Science to explore the future of diagnostics in the NHS reported that barriers to the adoption of diagnostics included hospitals requirement for the same level of evidence for diagnostics as for pharmaceuticals, while the clinical trial research infrastructure was less developed for diagnostics than for pharmaceuticals.[40]

Disruption in team routines and interactions

Using POCTs in general was not seen as disruptive in both countries, even if "it takes a bit more time" to use the tests (nurse 2-England).

Work needed to implement change

Several participants in both countries mentioned that the work needed to implement the tests after hospital-level approval requires substantial work and is often underestimated:

> "It sounds simple but the administration, the quality you have to ensure, the maintenance… that's very demanding. People underestimate the time you need for all of this" (head of laboratory 3-Netherlands).

6.4.3.6. The wider system

Policy context

Policies pertaining to antimicrobial resistance (AMR) were examined because an expected impact of CRP POCTs is the reduction of antibiotic use. In hospitals, alternatives to CRP POCTs, such as laboratory-measured CRP, microbiology, and observing/admitting the patient are available; however, in busy periods of the year, CRP POCTs may help to expedite the decision to prescribe antibiotics or not. The Dutch AMR policies recommend the use of new diagnostics in general to mitigate AMR but does not specifically mention POCTs.[41] In England, the UK AMR policy supports the use of POCTs, but does not mention CRP nor any specific biomarkers.[42]

Policies pertaining to the time spent by patients in EDs were also examined because several participants mentioned that improving the flow of patients was one of the most important potential values of CRP POCTs. In the Netherlands, there is no such policy.[43] In contrast, in England, the NHS has introduced waiting time standards in 2004 to reduce ED overcrowding. Their aim is that 95% of people attending ED are seen within four hours.[44] Hospitals that did not reach those targets endured a financial fine. One head of an ED in England mentioned that this was an important reason to pilot the test in his department. The fines were removed in 2016, but the 4-hour limit remains as a standard for English ED services.[45]

We also examined strategies for consolidation of laboratory services, as some participants reported that laboratory consolidation was a driver of POCTs implementation. In England, following the publication of two independent reviews the NHS promoted the centralisation of some laboratory analyses in central hubs to reduce the cost of pathology services.[46,47] Similarly, this approach was adopted in other European countries during the last decade, including the Netherlands.[48,49]

Economic context

Containment of healthcare costs is a common challenge across European countries, particularly since the 2008 economic crisis.[50] However, cost-containment has been particularly important in the UK.[32,50] As a result, health expenditure per capita in the UK is 16% lower than in the Netherlands,[51] and several participants reported that containment of

healthcare cost is an important barrier to the introduction of innovations in general in the NHS.

Regulatory context

The 12 quantitative CRP POCTs are CE marked in accordance with the European Union IVD Directive (98/79/EC).[20] CE marking is a process through which the manufacturer self-declares that the device conforms with EU regulatory standards.[52] This allowed manufacturers to commercialise the tests legally in the EU, including the Netherlands and England (until December 2020 for the latter).

Role of professional bodies

As mentioned earlier, the use of CRP is recommended in guidelines from the Dutch Paediatric Association, NICE, and the RCPCH, although none mention the use of CRP POCTs specifically. The role of these bodies in both countries on hospital adoption of tests such as CRP POCTs is limited because the inclusion of a relatively cheap diagnostic test (cheap compared to, for example, the use of CT-scan) in a guideline has limited influence on the definition of the DRG reimbursement groups and their price.[39]

Interorganisational networks

In both countries, few participants mentioned that they exchange knowledge and experiences about the introduction of new diagnostics through informal and formal professional networks. Among the formal organizations, there are regional support structures that help disseminate healthcare innovations, such as ROS Robuust in the Netherlands and the Academic Health Sciences Network in England.[53,54] The Oxford AHSN led the pilot study in three English hospitals mentioned in section 6.4.3.3.

6.4.3.7. Adaptation of the technology over time

CRP POCTs devices cannot be physically changed or adapted. However, there have been attempts to adapt the use of CRP POCTs by incorporating the tests into a clinical tool that predicts the risk of severe infections in febrile children presenting to EDs, combining clinical

signs and CRP results in one score. One such study including Dutch and English febrile children, accurately predicted the risk of severe infection.[18] However, the use of the tool did not reduce length of stay or antibiotic use in febrile children in two recent trials conducted in the Netherlands.[55,56]

6.4.4. Discussion

6.4.4.1. Summary of principal findings

Our study suggests that the main explanators of the higher availability of CRP POCTs in hospitals in the Netherlands compared to England lie at the micro and macro levels. Most hospital healthcare workers in the Netherlands are familiar with CRP POCTs because the tests are widely used in primary care, and healthcare workers often see patients referred by GPs with CRP POCTs results. This familiarity made most healthcare workers believe that CRP POCTs are dependable diagnostics. In contrast, in England, where the tests are less available in primary care, most participants expressed doubts about the reliability of the technology. This is an important difference because healthcare workers usually initiate the process of implementing new diagnostics.

In terms of the macro level, although hospital diagnostics are funded through similar Diagnosis Related Group reimbursement mechanisms in the two countries, the actual funding for healthcare is more constrained in England. This can result in more scrutiny and the use of stricter clinical and cost-saving criteria during the decision-making process to adopt diagnostic tests. This can lead to the multiplication of pilot studies and is an important barrier to the implementation of new diagnostics including CRP POCTs.

There are neither substantial nor consistent differences between countries in terms of the burden of the condition, the value of CRP POCTs for industry, users or patients, and the impact of CRP POCTs on the identity or practices of healthcare workers. Hospitals adapted to the increased demand for POCTs in both countries by assigning laboratory personnel to manage POCTs outside of the laboratories, although this process seems more advanced in the Netherlands. There are similarities and differences in terms of high-level policies and standards. The consolidation of laboratory services has been promoted in the two countries over the last decade in a similar way. However, the AMR policies differ: in England policies

recommend the use of POCTs (although not specifically CRP POCTs) while in the Netherlands they only mention diagnostics in general. There are standards regarding the time spent in EDs in England, but there is no equivalent in the Netherlands. The AMR policy and ED attendance time standards could have led to more adoption of CRP POCTs in England than in the Netherlands; the fact that this did not happen suggests that there may be a disconnect between high-level policies and what effectively happens in health services, and/or that the introduction of new diagnostic tests is comparatively more difficult in England.

Although we primarily examined the reasons for the different levels of adoption of CRP POCTs in hospitals in the Netherlands and England, it is worth noting that the tests are less often adopted in hospitals than in primary care in both countries. Our study suggests that this is because in most hospitals the laboratory-measured CRP provides an alternative to CRP POCTs. In addition, hospitals receive a fixed sum of money for each clinical case via the Diagnosis Related Group funding mechanism. This encourages hospitals in both countries to use fewer and cheaper diagnostics to ensure the reimbursement covers the actual cost of care, which favours laboratory CRP being cheaper than CRP POCTs. However, CRP POCTs can be useful in other hospitals, such as hospitals where the laboratory cannot provide CRP levels 24/7, hospitals where the turnaround time is long, which affects the flow of patients in EDs, and hospitals where the ED resources (personnel and infrastructure) are limited and expediting patient care is particularly important. The higher availability of CRP POCTs in hospitals in the Netherlands compared to England presumably occurs in those types of hospitals.

6.4.4.2. Comparison with other literature

In the Netherlands, a survey of GPs found that 80 % of GPs use CRP POCTs,[57] and it has been described that there is a strong integration between primary and secondary care with most hospitals involved in the provision of services to primary care,[58] including the implementation of CRP POCTs in GP practices. The widespread adoption of CRP POCTs in primary care and the better integration of primary and secondary care supports our finding that hospital healthcare workers in the Netherlands are more familiar with CRP POCTs.

This study suggests that introducing POCTs was more challenging in England than in the Netherlands. The most recent UK National Action Plan against AMR suggests that the

adoption of novel diagnostics in the NHS was difficult.[59] Funding constraints in England were an important barrier to the implementation of CRP POCTs in this study. An independent review of the introduction of innovations in the English NHS found that funding restrictions were limiting the adoption of innovations. The review found that hospitals need to prioritise investment in innovations, which leads some hospitals to apply high standards of clinical and cost-effectiveness, "sometimes hardly attainable", before deciding to adopt an innovation, which is in keeping with our results.[60] Another report describing child healthcare in the UK suggests that this may even result in some rationing of care.[61] A recent qualitative study about the barriers to the implementation of POCTs in England found that cost was one of the two most cited barriers.[62]

6.4.4.3. Strengths and limitations

To the best of our knowledge, this is the first study to comprehensively compare the adoption of CRP POCTs in hospitals in two countries. Using the NASSS framework allowed us to conduct an in-depth, wide-ranging, and consistent comparative health systems analysis. We conducted a document analysis in combination with interviews of a wide range of stakeholders in the two countries which allowed us to triangulate the findings presented in this article. Moreover, most studies on the adoption of CRP POCTs focus on the adoption of tests in adult patients in primary care; this is one of few studies focusing on the adoption of tests for the management of acute childhood infections in hospitals. Our findings should be interpreted in light of some limitations. The sample size was small for some of the subgroups of stakeholders, particularly at the macro level, although this was mitigated by the extensive review of documents which allows a comprehensive understanding of the macro level aspects at stake. We were unable to interview children and their carers, whose contributions could have provided important additional information. The background and experience of using POCTs by some of the authors may have influenced the interpretation of data towards a positive perception of the role of diagnostics and POCTs in clinical practice, despite the best attempts to limit this.

6.4.4.4. Implications for organisations implementing POCTs and future research

Organizations considering implementing POCTs in hospitals should carefully consider how the implementation of the tests realistically fits with the potential users' perceptions of dependability and utility and, the reimbursement mechanisms for diagnostics.

The cost-effectiveness of CRP POCTs compared with traditional central laboratory testing in the management of acute childhood infections in the ED is unclear and warrants further evaluation and should incorporate a range of outcomes both at the level of the individual patient and the health service. Additional comparative analyses with other POCTs in other countries with different health systems arrangements would be useful to provide further insights to inform the implementation of current and future POCTs.

6.4.5. Conclusion

CRP POCTs appear to be more widely available in hospitals in the Netherlands because of the greater familiarity of Dutch healthcare workers with CRP POCTs and because there are more funding constraints in England. Most hospitals in the Netherlands and England have not adopted CRP POCTs because the alternative CRP measurements from the hospital laboratory are available in a few hours and at a lower cost.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the London School of Hygiene & Tropical Medicine Ethics Committee (Ref:15040-15088). All methods were performed in accordance with the relevant guidelines and regulations of the London School of Hygiene & Tropical Medicine Ethics Committee. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the London School of Hygiene and Tropical Medicine Compass data repository (https://datacompass.lshtm.ac.uk).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Juan Emmanuel Dewez (JED) and Shunmay Yeung (SY) conceived the study. SY obtained funding for the study. All authors input into the design of the study. JED developed the initial study materials with inputs from SY, Ruud G Nijman (RGN), Edmond Li (EL), Queen Luu (QL), and Marieke Emonts (ME). JED conducted the searches to identify documents. RdG, MvdF, and RP identified the initial stakeholders in the Netherlands. JED, SY, RGN, ME identified stakeholders in England. JED conducted all the interviews in the Netherlands, SY participated to two interviews, RGN participated to one interview. EL and QL conducted the interviews with doctors and nurses in England under the supervision of JED, JED conducted the remaining interviews. JED conducted the thematic analysis with cross verification from EF, and inputs from all co-authors. JED drafted this manuscript which was reviewed and edited by all co-authors.

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Research team

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6.5. Supplementary materials

Supplementary materials 1. Topic Guide (paediatrcians): Adoption of C-reactive protein rapid tests in hospitals

Participant ID Number:	Gender: Male / Female
Country:	Date

Introduction:

- Overview and purpose of study
- Introduce who is involved in this study
- Aims of interview and expected duration
- Explain why participant has been selected
- What will happen to the results of this study
- Solicit questions
- Go through consent form with participant

Warm-up and general information:

What is your role in the hospital? In which department(s) do you work? When did you graduated? Which rapid POCTs are available? How many devices are available? Turnaround time for routine laboratory tests (eg CRP, full blood count, chemistry)?

Topics	**Questions**
1. Current practice	A 4-month-old infant presents to your emergency department with fever, asymptomatic otherwise, clinical examination unremarkable. The infant was inconsolable all morning, but currently settles with mum and feeding well, 3 non-bilious, milky vomits, vitals are within normal limits. Mum says he never vomits after feeds. • How would you manage this patient? • What are challenges, if any when seeing a child with acute fever? • What factors influence your decision to:

	○ Discharge the patient home or admit into the hospital? ○ Use/not use antibiotics? ○ Use diagnostic tests? If yes, which tests? And why?
2. The technology and its value	• Have you used CRP POCT? • If yes in which circumstances? • What were the advantages/disadvantages of using CRP POCT? ▪ For you? ▪ For the department(s) where your work? • Have you used them in children? ▪ If yes, what were the advantages/disadvantages of using CRP POCT in children? ▪ If no, why? • How did parents/children perceive the use of CRP POCT? • If no, why? • If because tests are not available, let's imagine the test are made available. • In which circumstances would you use the tests? • What would be the advantages/disadvantages of using CRP POCT? ▪ For you? ▪ For the department(s) where your work? • Would you use them in children?

	▪ What would be the advantages/disadvantages of using CRP POCT in children? • How would parents/children perceive the use of CRP POCT?
3. The adopters and the impact of CRP POCTs	• What changes, if any, did the use of CRP POCT brought/would bring to: o the way you work? o Your role in the department/hospital? • Was the test accepted/ would the test be accepted by parents/children? • Why yes/no?
4. The department/hospital	• How innovative in general is the department where you work? The hospital? • Can you tell me about an innovation that was introduced when you were working here? What happened? • How ready was/is the department/hospital for the introduction of CRP POCT? • What problems did you encounter/would you encounter in the implementation of CRP POCT? • Who decided/would decide whether the test should be adopted? • What are the criteria to decide to adopt tests such as CRP POCT?

	• How are/would be the cost of using the test be covered? • What impact did/would the use of CRP POCTs have on the way your department is organised? On the relation with other departments (eg the lab)? • What work was/would be needed to adopt the test once the decision to implement it is taken? • What were/could be the main challenges in this process?
5. The wider context	• Are you aware of the AMR policy of your country? • What impact does it have on your willingness to implement/use CRP POCT? • What impact does it have on your prescription of antibiotics? • Are there other policies that have an impact on the use of diagnostics/antibiotics? • What about the 4-hour waiting time policy? • What role, if any, did your professional association had /could have on the process of implementing tests such as CRP POCT? • How do you get to know about innovations? How is the knowledge about innovations disseminated across departments/hospitals?
6. Adaptation over time	• Has the use of CRP POCT changed since you started using it? Why?

	• How do you think the use of the tests would evolve if you started using it? • What could change the availability and use of CRP POCTs in the future?

End of interview:

- Ask participant if he/she has any question
- Ask if there is another relevant person he/she would recommend interviewing
- Ask if there is any document/website he/she would recommend accessing
- Thank participant.

Supplementary materials 2. Identification of documents for the document review

1. Criteria for considering documents for this review

Documents were included if they pertained to the adoption of diagnostic tests in hospitals in the Netherlands and England. This included:

- Publications in medical and health systems journals
- Clinical guidelines
- Information for patients about the use of diagnostic tests in hospitals
- Reports and recommendations of organisations involved in the organisation, funding, regulation, delivery, or evaluation of hospitals, with a focus on the implementation of diagnostic tests
- Policies with an impact on the implementation of innovations in hospitals
- Proceedings of conferences on diagnostic tests

2. Search methods for identification of documents

Documents were identified through a multi-pronged approach consisting of:

- Searching databases:
    - Pubmed
    - Google

- Searching websites of organisations involved in the organisation, funding, regulation, delivery, or evaluation of hospitals in the Netherlands and England:
    - Hospitals
    - Clinical commissioning groups (in England only)
    - Health insurance companies (in the Netherlands only)
    - Professional associations of Paediatrics
    - Organisations developing clinical guidelines
    - Local, national, and European health authorities
    - Independent organisations advising these health authorities
    - Agencies in charge of regulating the provision of healthcare
    - Agencies setting tariffs for medical procedures and technology
    - Independent organisations conducting health technology assessments
    - Independent organisations assessing health systems
    - Independent organisations in charge of disseminating innovations in health services
    - the European, Dutch and English in-vitro diagnostics industry
- Asking relevant documents to the 21 interviewees
- Attending relevant meetings and conferences about the implementation of diagnostic tests in health services
- Searching reference lists of identified documents

The search of data bases and websites were based on the following domains of enquiry:

13. Adoption (i.e., availability and/or use) of diagnostic tests
14. Epidemiology of fever in children
15. Care pathways for febrile children
16. Clinical performance, clinical effectiveness, and cost effectiveness of using CRP POC tests in hospitals
17. Organisation of hospital services
18. Funding of diagnostic tests in hospitals
19. Regulation of the use of diagnostic tests in hospitals
20. Policies pertaining to antimicrobial resistance and dissemination of technologies in health services

The search was based on a combination of medical subheadings (MeSh), key words, and synonyms for each of the domains of enquiry. The combination of search terms varied and was adapted to ensure it was relevant to the content of each database and websites (e.g., search terms pertaining to funding of diagnostics were used only in websites of organisations involved in the funding of health services).

There were no language restrictions. The search was conducted between 2019 and 2022 and was restricted to documents published after 2000.

Chapter 7. Discussion

This chapter presents the key findings from the three studies, an overall synthesis and interpretation of the findings, a comparison with other studies, the main strengths and limitations of the thesis, the implications of the findings for stakeholders involved in the implementation of rapid diagnostic tests, and the implications for future research.

7.1. Key findings

The aim of the thesis was to address evidence gaps about the factors which contribute to the adoption of POCTs for the clinical management of acute childhood infections in European settings. The thesis addresses four main knowledge gaps (Table 12):

1. What the variability is in the availability and use of POCTs for the clinical management of acute childhood infections across European countries
2. What the main determinants of this variability are
3. Why the adoption of CRP POCTs is different in primary care in two countries with similar healthcare systems
4. Why the adoption of CRP POCTs is different in hospitals in these two countries

Findings

1. The availability and use of POCTs for the clinical management of acute childhood infections varies substantially across European countries.

The first study of this thesis was a quantitative cross-sectional survey of European paediatricians which aimed to estimate the availability and use of nine POCTs. The availability and use of POCTs varies substantially across Europe. The most commonly available POCTs are urine dipsticks, which are available in over 80% of primary care practices and hospitals. The availability of other tests varied more, especially for CRP POCTs. Most paediatricians (69% in primary care and 80% in hospitals) reported that they would use a diagnostic test in the clinical scenario of an infant with undifferentiated fever. Urine dipsticks, CRP, and influenza were the most cited POCTs.

Table 12. Overview of evidence gaps, key findings, and implications for policy makers, regulators, industries developing POCTs, healthcare organisations, and healthcare workers.

Evidence Gaps	PhD Objectives	Methods	Key Findings	Research Papers	Implications
The availability and use of POCTs for the clinical management of acute childhood infections in European countries seems to vary across countries, but current estimates for most countries are not available.	1.To estimate the variability in the availability and use of POCTs for the clinical management of acute childhood infections across European countries.	Quantitative cross-sectional survey of primary care and hospital European paediatricians.	• The availability and use of POCTs varies substantially across Europe in primary care and hospitals. • Urine dipsticks are the most commonly available POCTs in primary care and hospitals. UD, CRP, and influenza are the POCTs that paediatricians would use more for infants with undifferentiated fever.	Paper 1 (Chapter 4)	POCTs are adopted in a wide range of European settings. Understanding the factor that influence the adoption of POCTs across the variety of European health systems can generate knowledge that is useful for informing the adoption of current and future POCTs.
The determinants of this potential	2. To identify the determinants of this variability	Multilevel logistic regression analyses to assess the	• The country of work predicts better the adoption of POCTs than workplace or healthcare workers characteristics.	Paper 1 (Chapter 4)	Industry, healthcare organisations, and healthcare workers keen to implement POCTs in primary care and hospitals in European countries must be aware that determinants at the

variability are unclear.	across European countries.	contribution of factors to the adoption of POCTs at two levels: 1) workplace and clinician level; 2) country of work level.			macro level are more influential for the adoption of POCTs than determinants at the meso and micro levels of health systems.
CRP is one of the most used and studied biomarkers for the management of acute infections. Its availability varies across countries and little is known about the factors that contribute to the availability and use of CRP POCTs in	3.To generate an in-depth understanding of the factors that contribute to high- versus low-level availability of CRP POCTs in primary care in two countries with similar primary healthcare systems, and to explore whether the	Comparative qualitative case studies in primary care settings based on document analysis and in-depth interviews with stakeholders in the Netherlands and England. The study was informed by the non-adoption, abandonment,	• CRP POCTs are more widely available in primary care settings in the Netherlands than in England mainly because of the interplay between early adopters and factors at the macro level of health systems. • In the Netherlands the use of CRP POCTs is partly reimbursed via a fee-for service scheme. The reimbursement mechanism was created because the use of CRP POCTs is recommended in clinical guidelines, which thus mandated their reimbursement, according to Dutch regulations. • The greater integration within and between primary and secondary	Paper 2 (Chapter 5)	**Implications for policy and regulation:** • Policies that promote the adoption of POCTs should be supported by specific funding for the implementation of the tests. • Policies that promote the integration of health services may contribute to the adoption of POCTs by allowing the exchange of knowledge and expertise, as well as operational support. • Standards (including clinical and cost effectiveness standards) to guide commissioners in their decision to adopt diagnostics, including POCTs, must be developed.

children in primary care.	tests are used in children.	scale-up, spread and sustainability (NASSS) framework.	care in the Netherlands is another important factor because it allows for a better operational support from laboratories to GP practices. • There are more funding constraints in England. This leads to a prioritisation of cheaper antimicrobial stewardship measures over POCTs. • The availability of CRP POCTs for their use in children is a by-product of the tests being made available for adults. The tests are less used in children by GPs because of the perceived uncertainty regarding the accuracy and effectiveness of using the tests in children, the lack of guidelines, and the perceived invasiveness of finger pricking.		**Implications for industry, healthcare organisations, and healthcare workers:** The implementation of POCTs must be informed by a good understanding of the following factors: • The funding landscape for diagnostics and POCTs, whether it is favourable or whether it could become favourable. • The current reimbursement mechanisms for diagnostics, the likelihood that a specific reimbursement scheme for POCTs could be developed, and what is needed to develop such as scheme. • The level of integration between health services and how this can support the implementation of POCTs. • The priorities of commissioners of healthcare, in light of the burden of diseases of the country or region • The buy-in from healthcare workers and patients regarding the use of POCTs, and how to increase it, if needed.

The availability of CRP POCTs in hospitals also seems to vary across Europe. The factors that contribute to the availability and use of CRP POCTs in children in hospitals might be different to those at play in primary care and are unknown.	4. To generate an in-depth understanding of the factors that contribute to different levels of availability and use of CRP POCTs in hospitals in the same two countries.	Comparative qualitative case studies in hospitals based on document analysis and in-depth interviews with stakeholders in the same two countries. The study was also informed by the NASSS framework.	• The availability of CRP POCTs in hospitals is greater in the Netherlands than in England because of factors that lie at the micro and macro levels of health systems. • Most hospital-based healthcare workers in the Netherlands are familiar with and trust CRP POCTs because the tests are widely adopted in primary care. • The funding constraints in England may lead to more scrutiny in the decision-making process for introducing innovations, including CRP POCTs. • CRP POCTs are adopted less in hospitals than in primary care settings in both countries because the funding of diagnostics is included in the fixed case-based reimbursement system (DRG based) that funds hospitals; this incentivises hospitals to use fewer and cheaper diagnostics, and CRP measured by the hospital laboratory is cheaper than CRP POCTs.	Paper 3 (Chapter 6)	**Implications for policy and regulation:** • As for primary care settings, the provision of financial support to back policies, and the development of evidence standards to guide adoption. **Implications for industry, healthcare organisations, and healthcare workers:** • As in primary care regarding the need to understand the funding landscape for diagnostics, the priorities of commissioners, and the reimbursement mechanisms. • Stakeholders should explore whether cheaper laboratory-based alternatives to POCTs are in use, in order to assess whether implementing POCTs provides an added value. • As in primary care regarding the need to understand the buy-in from clinicians and patients and how to improve it, if needed.

2. The country of work, including the macro level of health systems, better predicts the adoption of POCTs, than the meso or micro levels.

The multi-level logistic regression analysis from the first study showed that the country of work better predicts the adoption of POCTs than workplace or healthcare worker characteristics. However, the effect of country of work could not be explained by the country-specific factors that were available for this study, such as healthcare expenditure per capita or the main source of financing. The effect of the country of work operates through other factors.

3. CRP POCTs are more widely available in primary care in the Netherlands than in England mainly because of the interplay between early adopters and factors at the macro level of health systems.

The second study was a qualitative comparative study aiming to understand the factors that contribute to high versus low level of adoption of CRP POCTs in primary care in the Netherlands and England.

The study suggests that a more favourable macro level environment in the Netherlands allowed early adopters of CRP POCTs to successfully advocate for the adoption of the tests. In both countries, early adopters generated robust clinical and cost-effectiveness evidence about the use of CRP POCTs to reduce antibiotic prescription in adults with respiratory infections. This, combined with the advocacy of the early adopters led to the inclusion of CRP POCTs in the recommendations of national clinical guidelines in the two countries. In the Netherlands this led to the development of a fee-for-service reimbursement scheme which partially covers the use of the tests, because medical interventions that are included in clinical guidelines are mandatorily reimbursement under Dutch regulations. This regulatory context grants substantial power to primary care guidelines developers (who are almost exclusively GPs in the Netherlands) to influence the development of reimbursement schemes for primary healthcare.

By contrast, the tests were seen by GPs and commissioners as unwanted expenses in England, where the tests are not reimbursed despite being recommended in NICE guidelines, and where health services are under more important funding constraints. The funding

constraints result in the prioritisation of less expensive antimicrobial stewardship interventions, such as defining antibiotic use targets or benchmarking antibiotic use across different health services, which have effectively contributed to the reduction of antibiotic use in primary care in England.

Another important macro-level factor is the greater integration within and between primary and secondary levels of care in the Netherlands. This allows for a better operational support from primary care and hospital laboratories to GP practices for the implementation of diagnostic tests.

There are no substantial differences between England and the Netherlands in terms of the meso- or micro-level factors that could contribute to the difference in the adoption of CRP POCTs.

In terms of the adoption of CRP POCTs for the management of children with fever, the availability of the tests for their use in children is a by-product of the test being made available for adult patients, in both countries. GPs less frequently use the tests in children in both countries because of concerns about the accuracy, the clinical effectiveness, the cost effectiveness, the lack of guidelines recommending the tests for the paediatric population, and the perceived invasiveness of finger pricking in children.

4. CRP POCTs are more widely available in hospitals in the Netherlands than in England because of factors that lie at the micro and macro levels of health systems.

The third study was also a qualitative comparative study aimed understanding the factors which contribute to the different levels of adoption of CRP POCTs in the Netherlands and England, but in hospitals.

The main factors which explain the higher availability of CRP POCTs in hospitals in the Netherlands lie at the micro and macro levels.

In terms of at the micro level, most hospital-based healthcare workers (including clinicians and laboratory personnel) in the Netherlands are familiar with CRP POCTs and trust the tests because they are widely used in primary care. This familiarity made most healthcare workers

believe that CRP POCTs are dependable diagnostics. By contrast, in England, where the tests are substantially less used in primary care, most hospital-based participants expressed doubts about the reliability of the technology.

In terms of at the macro level, although diagnostics are funded through similar Diagnosis Related Group reimbursement mechanisms in the two countries, the actual funding for each hospital is more constrained in England. This may lead to more scrutiny and the use of stricter clinical and cost-effectiveness criteria during the decision-making process for adopting diagnostic tests, including CRP POCTs.

Although the level of adoption of the tests in hospitals is greater in the Netherlands, it is worth noting that the tests are substantially less adopted in hospitals than in primary care settings in both countries. The study suggests that this is mainly because hospitals are funded through fixed tariffs for each type of medical condition (the aforementioned Diagnosis Related Groups) in the two countries. This incentivises hospitals to use the least amount of medical procedures and equipment possible to ensure the fixed funding covers the actual cost of care, and even generates some profits. If there are more cost-effective alternatives for these medical procedures or equipment, the funding scheme incentivises the use of the cheapest one. In hospitals, unlike in primary care, there is a cheaper alternative to CRP POCTs, which is CRP being measured in the hospital laboratory. The latter is thus prioritised. However, CRP POCTs are still implemented in some hospitals because they can be useful in settings where the laboratory cannot provide CRP measures within a few hours and 24/7. The greater availability of CRP POCTs in hospitals in the Netherlands compared to England is likely the results of these circumstances.

7.2. Overarching interpretation

The overarching theme across the three studies is that the macro level of health systems seems to be more influential, although not exclusively, in the adoption of POCTs for the management of acute childhood infections than the meso or micro levels.

Within the macro level of health systems, reimbursement mechanisms appear to be an important factor. Fee-for-service schemes promote the adoption of services that are reimbursed, such as the use of CRP POCTs in primary care settings in the Netherlands. In

contrast, when funding is reimbursed through a fixed-sum system with no additional specific financial support (such as in the funding of the management of infectious diseases in primary care settings in England) or a fixed case-based reimbursement mechanism (such as in the funding of hospitals in the Netherlands and England), healthcare organisations are incentivised to limit the use of medical procedures and technologies to ensure the organisation does not spend more than it receives. This contributed to the lower adoption rates of CRP POCTs in primary care settings in England, as well as in hospitals in both the Netherlands and England.

The level of funding of health services can also play an important role when funding is more constrained, in that there is more pressure to prioritise certain medical interventions or approaches over others. This, in turn, can result in greater scrutiny during the decision-making process for adopting innovations. There seems to be a contradiction between the first study, in which health expenditure per capita was not found to be a determinant of the adoption of POCTs, and the two other studies, in which the greater funding constraints in England was identified as a barrier. This is due to the fact that the first study included several European countries, some of which have low levels of health expenditure per capita while the adoption of some POCTs is greater than in other countries. Focusing on two specific countries (the Netherlands and England) allowed for funding constraints to be identified as an important factor in these two countries, even though this factor appears to be less important within the wider picture across several European countries. This may be because of the greater role played by other factors in the adoption of POCTs in other countries, such as: 1) socio-cultural factors (including history, lifestyle); 2) structural factors which are external to healthcare (e.g., the political and economic environment); 3) international factors (e.g., new global evidence, efforts to harmonise healthcare across specific regions); and 5) specific situational events (such as the Covid-19 pandemic or local incidents in healthcare which prompted local changes).[1]

Another important factor seems to be the integration between healthcare organisations and services, which allows for the exchange of knowledge and expertise, as well as operational support.

The importance of the macro level does not mean that the micro level should be overlooked, however. Frontline healthcare workers are micro level actors who play a key role in initiating

the process of implementing diagnostics in their healthcare organisations. If healthcare workers are not interested or do not trust POCTs, it is unlikely that they will initiate or support the process that leads to the adoption of the tests. Moreover, even when POCTs are made available, the perception healthcare workers have of the tests plays an important role in their decision to eventually use them. This is evidenced by the example of CRP POCTs which even when available in primary care, are less used in children than in adults because of GPs' reservations regarding the use of the tests in children. Finally, as the comparative study of primary care settings suggests, early frontline users or early adopters can also play a catalytic role in actively generating evidence and disseminating it through all the relevant organisations at the micro, meso, and macro levels of the health systems.

7.3. Comparisons with other studies

In terms of the availability of POCTs for the management of acute infections in children, previous studies have been limited in either the range of POCTs examined, the number of countries included, or the predominant focus on adult patients. As outlined in the literature review in the introduction of this thesis, CRP POCTs are widely available in primary care practices in Scandinavian countries and the Netherlands, GAS POCTs are widely available in primary care practices in Scandinavian countries and France, and urine dipsticks are widely available and used in Northern European countries. Additional studies have been published since the studies for this thesis were conducted. Pandey and colleagues conducted a survey of 139 paediatric emergency departments in the UK and Ireland.[2] Urine dipsticks and blood gas analyses were the most commonly available POCTs, with the tests being available in 96.4% and 95% of hospitals, respectively. Influenza POCTs were available in 32.4% of hospitals and RSV POCTs in 29,5% of hospitals. CRP, procalcitonin, and GAS POCTs were the less frequently available tests, as they were only available in 9.4%, 1.4%, and 3.6% of hospitals, respectively. These findings are in line with the findings of the cross-sectional survey of this thesis with regards to the UK. In addition, in a survey of Spanish primary care paediatricians, Martin Peinador and colleagues found that GAS POCTs were available for 79% of participants, which is in keeping with the findings of this thesis with regards to Spain.[3]

In terms of identifying the levels of healthcare systems that are more influential for the adoption of POCTs, to the best of the PhD candidate's knowledge, no other studies have assessed this topic with a focus across several countries.

In terms of specific country factors that influence the adoption of POCTs, the comparative case-study of primary care settings of this thesis suggests that the fee-for-service reimbursement mechanism was an important factor which contributed to the adoption of CRP POCTs in the Netherlands. A recent Cochrane review found that fee-for-service payments increase the use of health services but may also lead to more unnecessary services being provided, which is in keeping with the findings of this thesis.[4] In addition, Huddy and colleagues exploring the facilitators of the adoption of CRP POCTs in a qualitative study found that the development of a specific reimbursement scheme for CRP POCTs use, facilitated by the support of professional organisations for early adopters, allowed for the implementation of the tests at scale in Scandinavian countries and in the Netherlands.[5] In another paper, the same authors identified eight groups of factors which play an important role in the adoption of POCTs: clinical, cultural, evidence, design and quality assurance, financial, organisational, patient, and other resource use factors.[6] The eight groups of factors overlap with the factors identified in the case-studies of this thesis. However, the aforementioned studies did not attempt to assess the relative importance of each group of factors, nor whether the factors at the macro, meso, or micro level of health systems contribute more to the adoption of POCTs. A recent comprehensive health technology assessment of CRP POCTs use in primary care settings examined the reimbursement of the tests in several European countries.[7] The assessment found that eight of the countries included in this thesis have specific reimbursement mechanisms for CRP POCTs in primary care: Germany, Hungary, Italy, Lithuania, the Netherlands, Poland, Slovenia, and Switzerland. The cross-sectional survey of this thesis found that CRP POCT were available in >60% of primary care paediatricians practices in five of these countries (Germany, Hungary, Lithuania, Slovenia, and Switzerland), which supports the finding of this thesis about the important role of reimbursement mechanisms.

Funding constraints in England were one of the major barriers for the implementation of CRP POCTs in the case-studies of this thesis. An independent review about the introduction of innovations in the English NHS found that funding restrictions were a major barrier to the adoption and spread of innovations in the NHS.[8] The review also found that some NHS organisations were using very high standards of evidence in the decision-making process for adopting medical innovations, comparable to those provided by randomised clinical trials, which are difficult to generate for implementors with limited resources. Another report describing child healthcare in the UK even suggests that there may be some rationing of care

because the provision of healthcare is restricted to interventions which are supported by available clinical and cost-effective evidence (Wolfe 2016).[9]

Finally, the lack of integration within and between primary and secondary care was identified as a barrier to the implementation of CRP POCTs in GP practices in England. The review mentioned in the previous paragraph also found that the fragmentation of the organisation of health services in 'silos' was impeding the adoption of innovations in the English NHS because of the lack of knowledge and expertise exchange.[8]

7.4. Strengths and limitations

The main strength of this thesis is the mixed methods design which combines breadth (the cross-sectional survey across different European countries) and depth (the case studies in the Netherlands and England) to estimate the extent and variability of the adoption of POCTs, as well as to understand the complexity of the interaction of factors which contribute to the adoption of POCTs. Moreover, the three studies were designed to ensure that data pertaining to the three levels of health systems, as well as to both primary and secondary levels of healthcare care were collected and included in the analysis. This allowed for a comprehensive analysis which could identify and hierarchise the main factors which contribute to the adoption of POCTs. The cross-sectional survey was developed through a robust process, such as the inclusion of the expertise of paediatricians from 11 European countries and the translation of the questionnaires into ten languages. The quantitative analysis was based on Bayesian MCMC methods to compute robust parameter estimates. The design and analysis of the qualitative case-studies were based on a framework which has been used in other studies to assess the adoption of innovations in health systems. Using the NASSS framework along with a combination of documents and interviews with a variety of stakeholders knowledgeable about the three levels of health systems, allowed for an in-depth, comprehensive, and consistent comparative health systems analysis. The combination of document analyses and interviews with a wide range of stakeholders allowed for the triangulation of the main findings. Finally, most studies on the adoption of POCTs focus on the adoption of the tests in adult patients; to the best of the PhD candidate's knowledge, this is the first assessment which focuses on the adoption of POCTs for the management of acute childhood infections.

However, the findings of this thesis should be interpreted in light of several limitations. The non-probabilistic nature of the sampling approach in the cross-sectional survey implies the possibility of selection bias: participants might have been more eager to use POCTs than other non-participating paediatricians, which may have caused an overestimation of the availability and use of POCTs in some countries. Other risks of bias such as social desirability, hypothesis guessing, and cultural bias are also possible.[10] While a large number of paediatricians participated in the studies, the pre-defined sample size for one of the analyses (the analysis of POCTs use) was not reached, which may limit the accuracy of the findings of this analysis. A specific clinical scenario was also used to explore the use of POCTs, which limits the generalisability of the findings for other scenarios. The case-studies were conducted in only two European countries and focused on one POCT, as conducting in-depth studies in additional countries would have required substantially more resources. This limits the generalisation of the case studies' findings to the Netherlands and England and to CRP POCTs. In addition, the small sample size for some of the subgroups of stakeholders who were interviewed, particularly at the macro level, may have introduced some participant bias, although this was probably limited by the triangulation of findings through the extensive document analysis. Children and their carers were also not included in this thesis because of the additional resources this would have required. This limits the data gained about the perspectives of children and carers, whose participation in the decisions pertaining to the provision of healthcare is increasing. In addition, the background with and experience of using POCTs of the PhD candidate and some of the co-authors may have created bias in the interpretation of data, towards a more favourable view of using POCTs, despite the best attempts to limit this. Finally, a major challenge facing health systems studies is that factors which are external to health systems may have an important influence on the organisation and delivery of health services. As mentioned earlier, there may be other factors beyond health systems factors which may play an important role in the adoption of diagnostics (including socio-cultural factors, external structural factors, international factors, and specific situational factors). These factors were not assessed in this thesis because this would have required more resources and expertise.

7.5. Implications for policy makers, regulators, industries developing POCTs, healthcare organisations, healthcare workers, and for future research

The Covid-19 pandemic has contributed to an increased awareness about the role and importance of diagnostics and POCTs. This could be seen as an opportunity for the implementation of POCTs which play a role in the management of infections. However, the focus may shift back to non-communicable diseases as the pandemic wanes and health services face the substantial unmet healthcare needs which have been caused by the pandemic. POCTs which can play a role in addressing these unmet needs might, thus, be prioritised, but this remains unclear. The findings of this thesis have several implications (Table 12) that are important for stakeholders involved in the adoption of POCTs. These implications, as well as recommendations for future research, are presented in this section.

7.5.1. Implications for policy

This thesis suggests that funding constraints can limit the adoption of POCTs. The AMR policy in England, which was one of the first to be published globally, promotes the use of POCTs but is not backed by specific funding. AMR policies in England and elsewhere, as well as other policies promoting the adoption of POCTs, need to be supported by financial means or incentives.

The integration of health services has been identified in this thesis as a facilitator for the adoption of diagnostics, including POCTs. Policymakers who are keen to support the adoption of POCTs should promote policies and initiatives aimed at developing the integration of health services, as this may contribute to an increase in the sharing of knowledge across different health services, as well as to the provision of operational support to health services keen to implement innovations.

7.5.2. Implications for regulators

In England the funding constraints may lead to greater scrutiny from commissioners in charge of deciding whether innovations should be implemented in primary care and hospitals. However, there are no clinical or cost-effectiveness standards to guide the decision to adopt diagnostics in healthcare services. This creates uncertainty in terms of the type of evidence that is required and may lead to the proliferation of pilot studies. Regulators in England and elsewhere should define those standards and ensure that they are adapted to local healthcare pathways and wider contexts. This would provide clarity for commissioners

and stakeholders who are keen to develop and implement diagnostic tests, by better informing their decision about whether or not to implement POCTs.

7.5.3. Implications for industries developing POCTs

Industries keen to develop POCTs for implementation in European countries should have a good understanding of the following factors:

1. The funding landscape for diagnostics and POCTs, whether it is favourable or whether it could become favourable. This would inform the selection of countries in which investments for the promotion and implementation of POCTs should be undertaken.
2. The priorities of commissioners of healthcare, in light of the burden of diseases in a given country or region. This would also inform the selection of countries.
3. The current reimbursement mechanisms for diagnostics, the likelihood that a specific reimbursement scheme for POCTs could be developed, and what is needed to develop such as scheme, including clinical and cost-effectiveness criteria and the role of clinical guidelines. This would allow industries to assess whether the funding of POCTs could be included in reimbursement schemes, as well as to identify actors involved in the development of such schemes.
4. The level of integration of health services and how this can support the implementation of POCTs. This would allow for an assessment of the requirements for engaging in the dissemination of knowledge about POCTs across health services and for providing operational support to organisations keen to implement POCTs.
5. The buy-in from healthcare workers (including nurses, doctors, laboratory personnel) and patients regarding the use of POCTs. This would inform industries about the need to increase healthcare workers and patients buy-in through the promotion of POCTs via sales or marketing approaches, if needed.

7.5.4. Implications for healthcare organisations

Healthcare organisations keen to implement POCTs should have good knowledge of the following factors:

1. The current reimbursement mechanisms for POCTs and the criteria for obtaining reimbursements, if any. This would allow healthcare organisations to assess whether they could obtain financial support from the main funders of healthcare or whether they would need to identify specific funding from other sources (including out of pocket payments from patients).
2. The availability of organisations in charge of interorganisational networking and/or operational support for the implementation of diagnostic tests. This would allow for the identification of organisations with expertise in this domain who could help in the process of adopting POCTs.
3. The buy-in from healthcare workers and patients regarding the use of POCTs. This would ensure that healthcare workers working in these organisations, as well as patients agree with the use of the new tests and that any existing concerns are addressed.

7.5.5. Implications for healthcare workers

Healthcare workers who are keen to implement POCTs in their health services should have a good knowledge of the following factors:

1. The priorities of commissioners of healthcare and potential competing alternatives to the use of POCTs, such as:
    I. Other antimicrobial stewardship measures which could compete with the use of POCTs in the management of infections.
    II. Laboratory-based diagnostic tests, in hospital settings.

2. As for healthcare organisations, the availability of organisations in charge of interorganisational networking and/or operational support for the implementation of diagnostic tests, as well as the buy-in from colleagues and patients regarding the use of POCTs, and how to improve it, if needed.

7.5.6. Implications for future research

Additional research is needed to inform the implementation of current and future POCTs. This includes:

- Studies to assess the clinical and cost-effectiveness of using CRP POCTs and other POCTs in the clinical management of children with acute infections in primary care and hospitals across European countries.
- Studies to identify the needs for POCTs of healthcare workers who see children in consultation, as well as the needs of children and parents.
- Studies to generate and in-depth evaluation of the implementation of the tests in contexts where health systems are organised differently than in the countries studied in this thesis. This includes European settings where other healthcare workers (nurses, primary care paediatricians) provide care to children, countries where hospital diagnostics are funded through means other than a fixed case-based system, or countries where health expenditure is mainly covered by private sources. Further studies should also be conducted in low and middle-income countries.
- Studies to understand the role of country level factors which are external to health systems in the adoption of diagnostic tests and POCTs. These factors include:
    - Socio-cultural factors that may influence key decision makers in considering rapid diagnostic tests as acceptable, important, and needed to improve clinical practice in a country, such as: history; religion; cultural norms such as individual freedom to take decisions versus hierarchical decision-making norms; adherence to clinical guidelines; tolerance to change; perceptions and standards of good clinical practice and the role of diagnostics on clinical practice and on the identity of healthcare workers; the influence of media; the awareness of stakeholders about new technologies, and the capacity and habit of stakeholders to disseminate new knowledge through activism.
    - External structural factors. These are factors that are external to health systems, such as: economic model and wealth of the country; the political environment including whether a country has a liberal decentralised political system or a more authoritarian top-down system; and the capacity to generate policies (for example to contain the spread of AMR) as well as the connection between high level policies front line health services.
    - International factors. This includes international influences such as the generation of new international evidence; or international initiatives that promote harmonization and unification across countries (for example the influence of European medical professional associations).

    - Specific situational factors. This could be local factors such the local level of AMR, or the rates of mortality and morbidity caused by AMR (countries or regions with high levels of AMR could be more eager to introduce rapid tests that can reduce the use of antibiotics)
- Studies to estimate the diffusion of novel POCTs across European countries as they become available, and to identify countries where to conduct the studies mentioned above.

7.6. Conclusions

The availability and use of POCTs for the management of acute childhood infections varies substantially across Europe. The adoption of POCTs is a complex phenomenon even though POCTs appear simple and easy to use. Factors at the macro level of health systems are more influential in determining the adoption of POCTs in European countries. The specific macro level factors that are at play may vary across countries with different health systems structures and processes. Should current POCTs and future POCTs be implemented, understanding these factors would be essential for informing their implementation.

7.7. References

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Chapter 8. Personal reflections

I started this work wondering whether the implementation of rapid diagnostic tests in health services would be easy, as I am interested in the adoption of technologies that could help frontline clinicians working in resource limited settings.

I soon realised that this was a very complex topic. My naive view was probably shaped by my professional background. As a clinician, I had a limited understanding of what makes a diagnostic test being an effective clinical tool. As many clinicians, I thought that a test with good sensitivity and specificity to identify a condition and/or a test that allowed improving clinical outcomes in randomised clinical trials was an obvious useful aid to clinical practice. Thus, I thought that implementing such a test would be straightforward and just a matter of convincing few influential people, such as the head of a clinical department. This thesis made me understand how simplistic this view was and that a test must have much more attributes to be implemented at scale. Diagnostic tests must be analytically accurate in measuring whatever they measure, clinically accurate in identifying a condition, clinically effective in changing patients' outcomes, good value for money, affordable, culturally accepted by healthcare workers, adapted to local care pathways and work routines, and not pose a threat to the identity or workloads of other healthcare workers. I also understood that people with decision-making power in terms of implementing diagnostic tests were scattered all across the different levels of health systems. The few decision makers at the micro level of health systems I was familiar with, had actually very little power and I realised that they were just secondary actors within a very complex context.

A favourable context is indeed a key determinant of the sustainable adoption of innovations. I understood through this work that the concept of context is actually much broader that the health systems context. As mentioned in chapter 7, it encompasses socio-cultural factors, non-health systems structural factors, international factors, and specific situational factors. I couldn't examine most of those factors because this would have required more resources and more expertise in other scientific domains. However, realising the importance of such factors was humbling in that it suggested that the work presented in this thesis mostly examines just a fraction of what determines the adoption of rapid diagnostic tests.

National contexts vary substantially across European countries. The recent decades of globalisation and expansion of the European Union may have contributed to some

standardisation in the way European countries are organised and function, including in terms of the delivery of healthcare. However, and in line with a substantial existing body of evidence about the diversity of European health systems, the work presented in this thesis, as well as additional work I carried out in other European countries, made me fully realise how diverse European health systems and health services are. Being aware of this diversity is essential because different strategies of implementation tailored to the context of each country are needed. To achieve this, ideally, stakeholders keen to implement rapid diagnostic tests, or any innovative technology, should undertake a comprehensive examination of the local context. However, the resources needed to do this are substantial and are not available to all stakeholders, particularly those working at the micro level, such as frontline paediatricians or GPs. Large multidisciplinary research consortia or large diagnostic test companies may have more resources to undertake such a big task. Collaboration between as many relevant stakeholders as possible is needed to comprehensively assess the relevant factors in a given country. However, building partnerships is not a straightforward process. I realised thought this work that most participants work in silos. Few participants had a transversal view about other stakeholders and factors, let alone stakeholders and factors in other countries. Most participants were aware of only the closest stakeholders they interact with for other purposes. This is understandable, as most participants do not need this transversal knowledge to perform their work and they have limited spared time, capacity, or incentives to expand their knowledge on this topic. Another barrier to building partnerships is the potential reservation of manufacturers and companies who commercialise diagnostic tests to engage in partnerships and share knowledge, as the latter is often considered as strategic market information.

Finally, the work presented in this thesis allowed me to better understand the relative importance, or lack of importance, of child healthcare among the priorities of healthcare decision makers in European settings. Being a paediatrician, having worked in low resource settings where around half of the population are children, and working for a research consortium focusing on improving the management of acute childhood diseases made me initially think that rapid diagnostic tests for acute childhood infections were obviously important. I soon realised that acute childhood infections are not a priority in European settings because their burden is small compared to that of adult chronic diseases. This is mainly because children represent only around 15 % of the European population and

because effective preventive measures, such as the use of vaccines, have, fortunately, made severe infections a very rare event. Acute childhood infections are a greater priority in low resource countries, but affordability is a main barrier, among other barriers that need to be examined, to the sustainable adoption of innovations by health services in those settings.