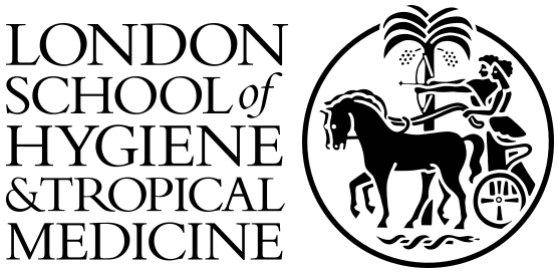

The availability and use of diagnostic tests for the management of acute childhood infections in Europe: the protocol for a cross-sectional survey of paediatricians.

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ABSTRACT

Introduction

Fever is a frequent reason of consultation in children, but correctly identifying the few febrile children with potentially severe bacterial infections is difficult. This encourages clinicians to prescribe empirical antibiotics and subject children to extensive and sometimes invasive testing. Rapid point of care tests (POCTs) are recommended internationally to reduce the use of antibiotics and medical resources. The extent of the availability and use of POCTs by paediatricians in Europe is unclear, but appears to vary widely across countries. The aim of this study is to document the availability and use of rapid POCTs for the clinical management of acute childhood infections and to identify factors associated with the variability of their adoption across Europe.

Methods and analysis

The study is an online cross-sectional survey of paediatricians working in primary care and hospitals in more than 24 European countries. Participants were recruited through several European research and clinical networks

Descriptive statistics will be used to describe the availability of rapid POCTs to paediatricians and the use of rapid POCTs in a clinical scenario of an infant with undifferentiated fever. Weighted regression analyses will identify factors of the availability and use of rapid POCTs across the included countries.

Ethics and dissemination

Participating to this anonymous survey does not carry any risk. Ethical approval was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee.

The results of the survey will be presented at European paediatrics conferences and submitted for publication in peer-reviewed medical journals. This study will contribute to understanding the reasons for the variability in the adoption of rapid POCTs across different countries. The findings from this study will be useful for clinicians, health services and the industry developing and implementing rapid POCTs, particularly for the clinical management of febrile children.

Key words

Acute febrile illness, point of care tests, diagnostics, paediatrics, child health

ARTICLE SUMMARY

Strengths and limitations of this study

- Paediatricians from 24 European countries were recruited through several pan-European research networks and national professional associations of general, infectious diseases, and emergency medicine paediatricians working at primary care and hospital levels
- The survey materials were developed through a robust process including the involvement of experts from 10 European countries, two pilot pre-studies, the translation of the questionnaires into 10 languages, and the use of a software which allowed several quality assurance checks, such as mandatory questions, adaptative questions, consistency and completeness checks, and the prevention of automated multiple entries
- The main limitation is the non-probabilistic nature of the sampling approach, which implies that there may have been selection bias
- Response rates may be low, given the online nature of the survey, and there is a risk of response fatigue, given the number of questions, which may have led to non-response bias and loss of statistical power
- We used one specific clinical scenario to explore the use of rapid POCTs, which implies that the findings of the study will not necessarily be generalisable to other clinical scenarios

INTRODUCTION

Fever is a frequent cause of consultation in children.[1] On average, children under five years of age experience two episodes of fever annually.[2,3] Most febrile children have an infection. Infections cause 32% of under-five deaths globally.[4] However, most infections in children are self-limiting.[5-7] Severe bacterial infections represent less than 1% of febrile children consulting in primary care,[5] and 7-15% of those presenting to emergency departments.[6,7]

Correctly identifying the few children with potentially severe bacterial infections is difficult.[5] At primary care level, clinicians have limited access to diagnostics and use their clinical expertise. However, history and physical examination may be unspecific.[5] As a result, antibiotics are often prescribed to ensure no potentially severe bacterial infections are left untreated.[8] On the other hand, some children who are developing an invasive bacterial infection may be sent home without treatment because they lack specific symptoms at the time of consultation.

At hospital level, clinicians often admit young febrile children to rule-out potentially severe infections. During the hospitalisation, children are monitored, and undergo several, sometimes invasive, diagnostic tests. It can take 48 hours or more for some of the tests such as blood cultures to return results. In the meantime, children receive broad-spectrum antibiotics, while most of them actually do not have a severe bacterial infection.[6,7] This approach can result in anxiety and discomfort for children and their parents, expensive hospitalisations,[9] and may contribute to the development of antimicrobial resistance (AMR).[10]

The World Health Organization recommends using rapid point-of-care tests (POCTs) to reduce antibiotic prescription because they can be easily performed and provide rapid results to aid clinical decision-making.[11] The use of rapid POCTs could also limit the use of other invasive tests, and allow a better use of medical resources.[12] There are three main types of rapid POCTs for the management of acute infections in children. The first are tests that detect the presence of a specific pathogen, such as group A Streptococci (GAS), or influenza.[13,14] The second type are tests that measure the host reaction to infection, such as tests measuring C-reactive protein (CRP), or procalcitonin (PCT).[15] These latter

tests are useful in febrile children with no other clinical signs to rule-in or out bacterial infections[16] and as an indicator of severity, even if the pathogen and/or the location of infection is not identified. The third type are tests that detect both the pathogens and the host reaction, for example urine dipsticks, which can indicate the presence of nitrites produced by bacteria, and of leucocyte esterase, an enzyme produced by the hosts during bacterial infections.[17]

The impact of rapid POCTs depends on several factors, including their analytical and clinical performance, but also their adoption by clincians.[18] For example, effective rapid POCTs to diagnose malaria are available. However, many clinicians in malaria-endemic countries prescribe antimalarials even when patients test negative, because they are reluctant to shift from reliance on clinician judgement, or mistrust test results.[19]

There seems to be a wide variability in the availability and use of rapid POCTs across Europe. However, evidence describing the availability and use is scarce and mainly limited to studies on the use of POCTs by General Practitioners (GPs) in adults in northern countries. These show that tests POCTs to detect GAS are widely used in France[20] and CRP POCTs are used in almost all GP practices in Sweden[21-25] and Denmark,[26] while the proportion of GPs which use the test is 3% in Belgium, 15% in the United Kingdom, and 48% of in the Netherlands.[27] Urine dipsticks seem to be widely used across Europe.[27-29] The availability and use of rapid POCTs in the management of febrile children across Europe is unclear, but also appears to vary. This variability could be explained by health systems and policy factors while the variability in the use of the tests could be due to characteristics of clinicians, such as specialization, or years of experience, and their attitudes towards rapid POCTs.

The aim of this study is to document the variability in the availability and use of rapid POCTs for the clinical management of acute childhood infections in Europe and to identify factors associated with the variability. The knowledge generated by the study will inform the development and implementation of current and future rapid POCTs in different European countries.

METHODS AND ANALYSIS

The study is an online cross-sectional survey of paediatricians working in primary care and in hospitals in Europe. Data collection was conducted between September and November 2019.

Outcomes

1. Primary outcomes:
    I. Proportion of participants who report the availability of CRP POCT in their workplace. CRP was chosen because it is one of the most widely used and researched non-specific tests for indicating bacterial infection and severity, and is a blood test (as are many of the new tests in development)
    II. In those reporting that CRP POCT is available in their workplace, the proportion of participants who report they would use it in a clinical scenario (i.e. a febrile infant with no clear focus)
2. Secondary outcomes include:
    I. Proportion of participants who would like specific rapid POCTs to be made available
    II. Proportion of participants who report the availability of other rapid POCTs (e.g. urine dipsticks) in their main workplace.
    III. Proportion of participants who report the use of diagnostic tests other than CRP POCT in the clinical scenario. Proportion of participants reporting different reasons for using diagnostic tests in the clinical scenario. Characteristics of future rapid POCTS for the management of acute childhood infections considered to be most important by participants.

Study setting

We aim to include clinicians providing healthcare to acutely ill children from any European country. The authors are members of several European paediatric research networks (see below) which between them have a strong presence in 24 countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Finland, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Switzerland, Ukraine, and the United Kingdom. We expect

that most participants will be from these targeted countries. These countries represent a wide spectrum of European countries in terms of potentially important characteristics, including who delivers most primary healthcare to children (paediatricians or GPs), and the financing mechanisms for health services.

Recruitment of participants

To be included, participants needed to fulfil the following criteria:

- Be a clinically active paediatrician providing acute care to children based either in primary care or in hospital
- Be a general paediatrician or paediatrician with a subspecialty or special interest (particularly in infectious diseases and emergency medicine)

We included both junior doctors and consultants, and doctors working in either the private or public sector in any European country. Paediatricians not clinically active or medical students were not included.

Participants were identified through the following networks:

- Personalised Risk assessment in febrile illness to optimise Real-life Management across the European Union (PERFORM) network, a European research consortium which aims to improve the clinical management of febrile children[30]
- European Academy of Paediatrics Research in Ambulatory Settings network (EAPRASnet)[31]
- European Society of Paediatric Infectious Diseases (ESPID)[32]
- Research in European Paediatric Emergency Medicine (REPEM)[33]
- National associations of paediatrics, paediatric infectious diseases, and paediatric emergency medicine from the countries listed above (Additional file 1)

Within each network, an authorised person emailed an invitation to all members, using internal email lists, except in the UK where the invitation was incorporated in the newsletter of the national association (Royal College of Paediatrics and Child Health). Three reminders were sent two weeks apart. Participation was monitored weekly, and in countries with low participation, national

coordinators, who were members of one of the above networks, further disseminated the survey locally through professional networks, or during conferences or workshops. In the UK, the survey was also disseminated by the national association's social media account. No incentives were offered to potential participants.

Sample size

The sample size was computed to allow estimation of the two main outcomes of interest (the availability of CRP POCT, and the use of CRP POCT in the clinical scenario) with a certain degree of precision (Table 1). We considered primary care and hospital paediatricians as two different populations because of the differences in the availability of diagnostics and the overall context of care in those settings, as well as different *a priori* chance of bacterial infection in children in these settings. We 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 1 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 1 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[34,35] (Table 2). We hypothesised that CRP POCT would be available to 50% of clinicians in the >2,800 Euros group based on the availability of CRP POCT in the Netherlands,[27] compared to 25% in the ≤2,800 Euros. The power to detect a difference between the two groups (with 252 primary care paediatricians in the ≤2,800 Euros category versus 241 in the >2,800 category, and 322 hospital paediatricians in the ≤2,800 Euros category versus 385 in the >2,800category, Table 2) 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.[36] We considered that 20% of the sample will have ≤10 years of experience, based on European figures of years of experience of medical doctors.[37] 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 median rate of CRP use in febrile infants from 11 European hospitals members of the PERFORM consortium (unpublished data). The power to detect a difference between the two groups (with 99 primary care paediatricians in the ≤10 years of experience category versus 394 in the >10 years of experience category, and 141 hospital paediatricians in the ≤10 years of experience category versus 566 in the >10 years of experience category, Table 3) would be 97% in primary care and 99% in hospital settings. Thus, the sample sizes in table 1 would ensure that the planned regression analyses have sufficient power.

Consent and confidentiality

The invitation email provided information about the identity of the research team, the aim and nature of the study, the reason for contacting the recipient, and the time needed to complete the questionnaire (approximately 10 minutes). The email included a weblink to access the online survey. The first page of the survey consisted of a participant information sheet which further informed participants about the anonymous nature of the survey, the storing of all data for 10 years in the London School of Hygiene and Tropical Medicine (LSHTM) secure data server, which is password protected and only accessible to Juan Emmanuel Dewez (JED) and Shunmay Yeung (SY). The page also contained a consent box that participants had to tick to confirm they agree to take part to the study and to access the website hosting the questionnaires.

Data collection tools

Data were collected through an on-line structured questionnaire. There were two questionnaires: one targeting primary care paediatricians and another for hospital paediatricians. Most questions

were identical in the two questionnaires (14 questions were different). The questionnaires were developed based on a literature review and had four sections (Additional file 2):

1. Section A: general characteristics of participants and their workplace
2. Section B: availability of rapid POCTs in the workplace
3. Section C: clinical scenario and use of diagnostics in the scenario
4. Section D: characteristics of future diagnostics that are important to participants

The actual number of questions varied from 43 to 58 questions, depending on how the respondent answered certain questions (i.e. selecting specific answers to some questions gave access to additional questions). Collaborators from the targeted countries tested the initial drafts and provided input to improve the relevance of the questionnaires for their countries. The questionnaires were piloted for the first time during the paediatric infectious diseases master course of the 2017 European Academy of Paediatrics annual conference with 58 attendees, and adapted after analysis to improve the clarity and relevance of questions. The survey was developed in English and translated into French, German, Greek, Hungarian, Italian, Latvian, Polish, Spanish, Slovenian, and Ukrainian by a bilingual translator. This was followed by a back translation into English by another bilingual translator blinded to the original version. Any disagreement was solved through discussion with collaborators from the respective countries. There were a few exceptions with no back translation: the translations into French and Spanish were made by JED, who was one of the main developers of the questionnaires, and checked for accuracy by collaborators from France and Spain; the Slovenian translation was made by a Slovenian collaborator and checked by two other collaborators without back translation. Collaborators from each country checked the final online versions and provided feedback to correct typographical and formatting errors. The final version was piloted in Norway and Slovenia in June-July 2019 with 115 participants who could provide feedback by email. No technical issues were reported during the pilot. A few typographical errors were corrected after the second pilot.

Software and data management

We used software developed by a professional company with a track record in conducting online surveys.[39-41] Questions were mandatory except three questions. Most questions were closed-questions with a single answer from a drop-down menu; six questions were open with free text answers. The order of questions was not randomised. Questions were displayed in 13 pages. Pages contained between 1 to 10 questions. Completeness of each page and accuracy of responses (e.g. some of the free text answers had to be numerical answers) was checked through JAVAscripts. Participants were able to return to previous questions and change their answers. Data were automatically saved into a database after completion of each page. There was no technical means to prevent multiple entries by the same participant. A challenge-response test (CAPTCHA) was mandatory at the beginning of the questionnaire to prevent automated multiple entries by a computer.

Analysis

Only complete questionnaires will be analysed. Questionnaires that were completed in less than two minutes will be excluded, as completing the questionnaire in less than two minutes is possible only if respondents do not fully engage with the questions and provide random answers.

There might be response bias related to characteristics of participants (e.g. there might be more younger respondents because of the online nature of the survey, or more participants with a special interest in, for example, infectious diseases). To address this, we will use non-response weighting[42] to weight the data to replicate the distribution of the different sub-groups (including age groups, subspecialty groups) in the total population of paediatricians per country, provided that auxiliary data on these characteristics are available. Moreover, there will be an over-representation of participants from smaller countries given that the sample sizes are similar while the total population of paediatricians per country vary widely (Table 1). To address this in the analyses that use combined data from several countries (e.g. means across group of countries) we will use population size weighting.[42] The population size weight will be combined with the non-response weight.

Descriptive statistics will be used to derive the proportions of participants with relevant characteristics (including country of work, years of practice, type of workplace, subspecialty, etc), response rates per research network, availability of rapid POCTs, use of diagnostic tests in the clinical scenario, proportion of participants who agree/disagree with reasons to use tests, and future characteristics (including purposes of new tests, time to get results).

Multiple logistic regression analyses will be performed to identify determinants of CRP POCT availability, and CRP POCT use in the clinical scenario for each level of care (primary care and hospital care). Expected explanatory variables are presented in table 4. Univariable analysis of the explanatory variable against the outcomes of interest will be performed initially to develop the model. Multicollinearity will be assessed to drop one of the pair of correlated variables. Data from questionnaires with missing independent variables or the outcome variables will not be used in the model. Given that all the hypothesised explanatory variables were identified through a review of the literature, they will all be included in the model *a priori* (except those that are highly correlated).,

All analyses will be performed with Stata 16.®

Patient and Public Involvement

Patients and the public were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

Participating to the survey does not carry any substantial risk. Paediatricians may feel that the research team is making judgements or evaluating the provision of care. To mitigate against this, it was clearly explained during the consent process that the aim of the study was not to assess the quality of care but to describe and understand the use of POCTs in the participants' workplaces. The inconvenience for participants of taking time away from work might be a minimal source of discomfort as the survey completion takes only about 10 minutes. All participants provided electronic written informed consent. Ethical approval was obtained from the LSHTM Ethics Committee (Ref: 15977).

The results of the survey will be presented at European conferences of paediatrics (ESPID and EAP) and submitted for publication in peer-reviewed medical journals. The results will also be presented at

the final meeting of the PERFORM consortium, which gathers stakeholders in the field of the management of acute childhood infections from across Europe. The datasets generated during the current study will not publicly available but will be available from the corresponding author on reasonable request.

DISCUSSION

This study will contribute to understanding the reasons for the variability in the adoption of rapid POCTs, the use of which is recommended internationally to improve the use of antibiotics and medical resources in general. The findings from this study will be useful for clinicians, health services and the industry currently developing or implementing rapid POCTs, particularly for the clinical management of febrile children. The identification of countries where rapid POCTs have been adopted will also inform the development of additional in-depth studies in those countries to learn more about the contexts, actors, and processes which led to the successful implementation of rapid POCTs in clinical practice.

Strengths

This is a survey of paediatricians from across Europe. We used several pan-European research networks and national professional associations of general, infectious diseases, and emergency medicine paediatricians working at primary care and hospital levels to reach out to a broad range of paediatricians in 24 countries. In our analytical approach we will use available data to attempt to estimate how representative our sample is of paediatricians in those countries, and we will also be specifically exploring the contribution of health system factors in influencing the availability of diagnostic tests.

The survey materials were developed through a robust process including the involvement of experts from 10 European countries, two pilot pre-studies, the translation of the questionnaires into 10 languages, and the use of a software which allowed several quality assurance checks, such as mandatory questions, adaptative questions, consistency and completeness checks, and the prevention of automated multiple entries.

Limitations

The main limitation is the non-probabilistic nature of the sampling approach, which implies that there may have been selection bias. Obtaining comprehensive sampling frames from each country to select participants randomly would have required a much greater level of engagement with local health authorities, which was not possible.

Response rates may be low, given the online nature of the survey,[43] and there is a risk of response fatigue, given the number of questions, which may have led to non-response bias and loss of statistical power. Other risks of bias common in surveys, including social desirability, hypothesis guessing, and cultural bias,[44] are also possible.

We used one specific clinical scenario to explore the use of rapid POCTs, which implies that the findings of the study will not necessarily be generalisable to other clinical scenarios.

Finally, GPs are also an important provider of healthcare to children in some countries. We did not approach GPs, because this would have required substantial additional resources.

Word count: 3,974

REFERENCES

1. Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. Family practice. 2005;22(4):367-74.
2. Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to paediatric emergency departments: 10 years on. Emergency medicine journal : EMJ. 2012 May;29(5):379-82
3. Alpern ER, Stanley RM, Gorelick MH, Donaldson A, Knight S, Teach SJ, et al. Epidemiology of a pediatric emergency medicine research network: the PECARN Core Data Project. Pediatric emergency care. 2006 Oct;22(10):689-99
4. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. The Lancet. 2016;388(10063):3027-35.

5. Van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mant D. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. Lancet (London, England). 2010;375(9717):834-45.
6. De S, Williams GJ, Hayen A, Macaskill P, McCaskill M, Isaacs D, et al. Accuracy of the "traffic light" clinical decision rule for serious bacterial infections in young children with fever: a retrospective cohort study. BMJ (Clinical research ed). 2013;346:f866
7. Nijman RG, Vergouwe Y, Thompson M, van Veen M, van Meurs AHJ, van der Lei J, et al. Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. BMJ : British Medical Journal. 2013;346.
8. Lucas PJ, Cabral C, Hay AD, Horwood J. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. Scandinavian journal of primary health care. 2015;33(1):11-20.
9. Leigh S, Grant A, Murray N, Faragher B, Desai H, Dolan S, et al. The cost of diagnostic uncertainty: a prospective economic analysis of febrile children attending an NHS emergency department. BMC medicine. 2019;17(1):48.
10. European Centre for Disease Control, European Food Safety A, European Medicines A. ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. EFSA Journal. 2017;15(7):e04872-n/a.
11. WHO. World Health Organization. Global action plan on antimicrobial resistance 2015. Available from http://www.who.int/antimicrobial-resistance/global-action-plan/en. Accessed 20/12/17.
12. Larsson A, Greig-Pylypczuk R, Huisman A. The state of point-of-care testing: a European perspective. Upsala journal of medical sciences. 2015;120(1):1-10.
13. Stewart EH, Davis B, Clemans-Taylor BL, Littenberg B, Estrada CA, Centor RM. Rapid antigen group A streptococcus test to diagnose pharyngitis: a systematic review and meta-analysis. PloS one. 2014;9(11):e111727.

14. Wilson ML. Malaria rapid diagnostic tests. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012 Jun;54(11):1637-41
15. Kapasi AJ, Dittrich S, Gonzalez IJ, Rodwell TC. Host Biomarkers for Distinguishing Bacterial from Non-Bacterial Causes of Acute Febrile Illness: A Comprehensive Review. PloS one. 2016;11(8):e0160278
16. Van den Bruel A, Thompson MJ, Haj-Hassan T, Stevens R, Moll H, Lakhanpaul M, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ (Clinical research ed). 2011;342:d3082.
17. Mambatta AK, Jayarajan J, Rashme VL, Harini S, Menon S, Kuppusamy J. Reliability of dipstick assay in predicting urinary tract infection. Journal of family medicine and primary care. 2015;4(2):265-8.
18. Horvath AR, Lord SJ, StJohn A, Sandberg S, Cobbaert CM, Lorenz S, et al. From biomarkers to medical tests: the changing landscape of test evaluation. Clinica chimica acta; international journal of clinical chemistry. 2014;427:49-57.
19. Burchett HE, Leurent B, Baiden F, Baltzell K, Bjorkman A, Bruxvoort K, et al. Improving prescribing practices with rapid diagnostic tests (RDTs): synthesis of 10 studies to explore reasons for variation in malaria RDT uptake and adherence. BMJ Open. 2017;7(3):e012973
20. Pulcini C, Pauvif L, Paraponaris A, Verger P, Ventelou B. Perceptions and attitudes of French general practitioners towards rapid antigen diagnostic tests in acute pharyngitis using a randomized case vignette study. Journal of Antimicrobial Chemotherapy. 2012;67(6):1540-6.
21. Engstrom S, Molstad S, Lindstrom K, Nilsson G, Borgquist L. Excessive use of rapid tests in respiratory tract infections in Swedish primary health care. Scandinavian Journal of Infectious Diseases. 2004;36(3):213-8.
22. Andre M, Vernby A, Odenholt I, Lundborg CS, Axelsson I, Eriksson M, et al. Diagnosis-prescribing surveys in 2000, 2002 and 2005 in Swedish general practice: consultations, diagnosis, diagnostics and treatment choices. Scand J Infect Dis. 2008;40(8):648-54.

23. Lindstrom J, Nordeman L, Hagstrom B. What a difference a CRP makes. A prospective observational study on how point-of-care C-reactive protein testing influences antibiotic prescription for respiratory tract infections in Swedish primary health care. Scandinavian journal of primary health care. 2015;33(4):275-82.
24. Neumark T, Brudin L, Molstad S. Use of rapid diagnostic tests and choice of antibiotics in respiratory tract infections in primary healthcare--a 6-y follow-up study. Scandinavian Journal of Infectious Diseases. 2010;42(2):90-6.
25. Tyrstrup M, Beckman A, Molstad S, Engstrom S, Lannering C, Melander E, et al. Reduction in antibiotic prescribing for respiratory tract infections in Swedish primary care- a retrospective study of electronic patient records. BMC infectious diseases. 2016;16(1):709.
26. Haldrup S, Thomsen RW, Bro F, Skov R, Bjerrum L, Sogaard M. Microbiological point of care testing before antibiotic prescribing in primary care: considerable variations between practices. BMC family practice. 2017;18(1):9.
27. Howick J, Cals JW, Jones C, Price CP, Pluddemann A, Heneghan C, et al. 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. BMJ Open. 2014;4(8):e005611.
28. Hadjipanayis A, Grossman Z, Del Torso S, van Esso D, Dornbusch HJ, Mazur A, et al. Current primary care management of children aged 1-36 months with urinary tract infections in Europe: large scale survey of paediatric practice. Archives of disease in childhood. 2015;100(4):341-7.
29. Schols AM, Stevens F, Zeijen CG, Dinant GJ, van Vugt C, Cals JW. Access to diagnostic tests during GP out-of-hours care: A cross-sectional study of all GP out-of-hours services in the Netherlands. The European journal of general practice. 2016;22(3):176-81.
30. PERFORM. Personalised Risk assessment in febrile illness to optimise Real-life Management across the European Union. Available from http://www.perform2020.org. Accessed 03/12/19.
31. del Torso S, van Esso D, Gerber A, Drabik A, Hadjipanayis A, Nicholson A, et al. European Academy of Paediatrics Research in Ambulatory Setting network (EAPRASnet): a multi-national general

453 paediatric research network for better child health. Child: care, health and development.
454 2010;36(3):385-91.
455 32. ESPID. European Society for Paediatric Infectious Diseases. Available from https://www.espid.org/
456 . Accessed 03/12/19.
457 33. REPEM. Research in European Paediatric Emergency Medicine. Available from: http://repem.net/
458 .Accessed 03/12/19.
459 34. OECD. Organisation for Economic Co-operation and Development. Health at a glance. Europe
460 2016. State of health in the EU cycle. Available from http://www.oecd.org/health/health-at-a-
461 glance-europe-23056088.htm . Accessed 03/12/19.
462 35. WHO. World Health Organization. Available from: https://www.who.int/countries/en/ . Accessed
463 03/12/19.
464 36. McGillivray DL, Roberts-Brauer R, Kramer MS. Diagnostic test ordering in the evaluation of febrile
465 children. Physician and environmental factors. American journal of diseases of children (1960).
466 1993;147(8):870-4.
467 37. Eurostat 2019. Available from
468 https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_rs_phys&lang=en
469 Accessed 03/12/19.
470 38. ECPCP. European Confederation of Primary Care Paediatricians 2018. Available from:
471 https://www.ecpcp.eu . Accessed 10/10/19
472 39. Grossman Z, Del Torso S, van Esso D, Ehrich JH, Altorjai P, Mazur A, et al. Use of electronic health
473 records by child primary healthcare providers in Europe. Child: care, health and development.
474 2016;42(6):928-33.
475 40. Hadjipanayis A, Grossman Z, Del Torso S, van Esso D, Dornbusch HJ, Mazur A, et al. Current primary
476 care management of children aged 1-36 months with urinary tract infections in Europe: large scale
477 survey of paediatric practice. Archives of disease in childhood. 2015;100(4):341-7.
478 41. Bielicki JA, Barker CIS, van der Velden AW, Sharland M, van Esso D, Hadjipanayis A, et al. Antibiotic
479 preferences for childhood pneumonia vary by physician type and European region. ERJ Open
480 Research. 2016;2(2):00001-2016.
481 42. European Social Survey. Weighting European Social Surveys Data. Available from:
482 https://www.europeansocialsurvey.org/docs/methodology/ESS_weighting_data_1.pdf .
483 Accessed 05/12/19.
484 43. Leece P, Bhandari M, Sprague S, Swiontkowski MF, Schemitsch EH, Tornetta P, et al. Internet
485 Versus Mailed Questionnaires: A Randomized Comparison (2). 2004;6(3):e30.
486 44. Choi BCK, Pak AWP. A catalog of biases in questionnaires. Prev Chronic Dis. 2005;2(1):A13-A.

AUTHORS STATEMENT

Juan Emmanuel Dewez (JED) and Shunmay Yeung (SY) conceived the study. JED and SY developed the initial study materials. David Bath (DB), Stefano del Torso (SdT), Marieke Emonts (ME), Zachi Grossman (ZG), Adamos Hadjipanayis (AH), Emma Lim (EL), Ruud G Nijman (RGN), Diego van Esso (DvE) contributed to the refinement of the study materials and developed the data collection plan. JED, Lucy Pembrey (LP), SY estimated sample sizes. JED, DB, Alec Miners (AM), RGN, LP, and SY developed the data analysis plan. ME and EL conducted the first pilot. JED supervised the second pilot. JED and DvE supervised data collection. SdT, ME, ZG, AH, EL, RGN, DvE, SY supported data collection. JED drafted this manuscript which was reviewed and edited by all co-authors.

All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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513 **ADDITIONAL FILES**

514 Additional file 1:

515 List of organisations that disseminated the survey

516 Additional file 2:

517 Questionnaire

518 **DATA STATEMENT**

519 The datasets generated and/or analysed during the current study will not publicly available but will be

520 available from the corresponding author on reasonable request.

521 **TABLES**

Table 1. 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[37,38*]	Sample size of primary care paediatricians	Total population of hospital paediatricians[37,38*]	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
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
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
Netherlands	NA	NA	1,751	65
Norway	NA	NA	875	63
Poland	5,040	67	9,905	67
Portugal	NA	NA	2,085	66
Slovenia	252	53	396	58
Spain	4,800	67	7,589	67
Switzerland	978	63	839	63
Ukraine	3,321	66	6,236	67
United Kingdom	NA	NA	10,464	67
TOTAL	17,514	1,002	76,600	1,478

NA: not applicable

*Except for Spain and Poland, where figures were not available and provided by local partners

Table 2. Expected number of participants and health expenditure per capita categories

Country	Health expenditure per capita per year category (Euros)[34,35]	Half of primary care paediatricians' sample size	Half of hospital paediatricians' sample size
Bulgaria	≤2,800	NA	32
Croatia		27	30
Cyprus		24	17
Greece		32	32
Hungary		31	32
Israel		30	32
Latvia		4	36
Lithuania		12	30
Malta		NA	18
Poland		33	33
Slovenia		26	29
Ukraine		33	33
Sub total		**252**	**322**
Austria	>2,800	30	31
Belgium		32	32
Finland		17	30
France		32	33
Germany		33	33
Italy		33	33
Netherlands		NA	32
Norway		NA	31
Portugal		NA	33
Spain		33	33
Switzerland		31	31
United Kingdom		NA	33
Subtotal		**241**	**385**
TOTAL		**493**	**707**

NA: not applicable

Table 3. 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	493	707
<10 years of practice (20% of any experience)[37]	**99**	**141**
>10 years of practice (80% of any experience)[37]	**394**	**566**

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Table 4. Explanatory variables for the logistic regression analyses

A priori explanatory variables of CRP POCT availability in primary care practices
1. Country reimbursement mechanisms for diagnostics
2. Country level of health expenditure per capita
3. Main type of healthcare worker in charge of providing primary care to children (e.g. Paediatrician or general practitioner)
4. Sector of activity (public or private)
5. Distance between workplace and the nearest external laboratory
6. Type of practice (solo or group practice)
7. Main type of healthcare worker in charge of taking bloods in children (e.g. doctor or nurse)
8. Turnaround time to get results of blood tests such as C-reactive protein or full blood count
A priori explanatory variables of CRP POCT availability in hospitals
1. Country reimbursement mechanisms for diagnostics
2. Country level of health expenditure per capita
3. Type of hospital (e.g. paediatric or general hospital)
4. Level of care (secondary or tertiary level of care)
5. Sector of activity (public or private)
6. Main type of healthcare worker in charge of taking bloods in children (e.g. phlebotomist, lab technician, doctor or nurse)
7. Turnaround time to get results of blood tests such as C-reactive protein or full blood count
A priori explanatory variables for determinants of CRP POCT use by primary care paediatricians
1. Years of practice since graduation from medical school
2. Sector of activity (public or private)
3. Distance between workplace and the nearest external laboratory
4. Type of practice (solo or group practice)
5. Main type of healthcare worker in charge of taking bloods in children (e.g. doctor or nurse)
6. Turnaround time to get results of blood tests such as C-reactive protein or full blood count
7. Duration of consultations in busiest weeks of the year
8. Current availability of CRP POCT
9. Participant's perceived prevalence of bacterial infection in the clinical scenario
A priori explanatory variables for determinants of CRP POCT use by hospital paediatricians
1. Subspecialisation or special interest of doctors
2. Type of hospital (e.g. paediatric or general hospital)
3. Level of care (secondary or tertiary level of care)
4. Hospital department where participant mainly work
5. Years of practice since graduation from medical school
6. Sector of activity (public or private)
7. Main type of healthcare worker in charge of taking bloods in children (e.g. phlebotomist, lab technician, doctor or nurse)
8. Turnaround time to get results of blood tests such as C-reactive protein or full blood count
9. Duration of consultations in busiest weeks of the year

10. Participant's perceived prevalence of bacterial infection in the clinical scenario

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