Antibiotic prescribing rate after optimal near-patient C-reactive protein testing in acutely ill children presenting to ambulatory care (ARON project): protocol for a cluster-randomized pragmatic trial

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ABSTRACT

Introduction Children become ill quite often, mainly because of infections, most of which can be managed in the community. Many children are prescribed antibiotics which contributes to antimicrobial resistance and reinforces health-seeking behaviour. Point-of-care C reactive protein (POC CRP) testing, prescription guidance and safety-netting advice can help safely reduce antibiotic prescribing to acutely ill children in ambulatory care as well as save costs at a systems level.

Methods and analysis The ARON (Antibiotic prescribing Rate after Optimal Near-patient testing in acutely ill children in ambulatory care) trial is a pragmatic cluster randomized controlled superiority trial with a nested process evaluation and will assess the clinical and cost effectiveness of a diagnostic algorithm, which includes a standardised clinical assessment, a POC CRP test, and safety-netting advice, in acutely ill children aged 6 months to 12 years presenting to ambulatory care. The primary outcome is antibiotic prescribing at the index consultation; secondary outcomes include clinical recovery, reconsultation, referral/admission to hospital, additional testing, mortality and patient satisfaction. We aim to recruit a total sample size of 6111 patients. All outcomes will be analysed according to the intent-to-treat approach. We will use a mixed-effect logistic regression analysis to account for the clustering at practice level.

Ethics and dissemination The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements. Ethics approval for this study was obtained on 10 November 2020 from the Ethics Committee Research of University Hospitals Leuven under reference S62005. We will ensure that the findings of the study will be disseminated to relevant stakeholders other than the scientific world including the public, healthcare providers and policy-makers. The process evaluation that is part of this trial may provide a basis for an implementation strategy. If our intervention proves to be clinically and cost-effective, it will be essential to educate physicians about introducing the diagnostic algorithm including POC CRP testing and safety-netting advice in their daily practice.

INTRODUCTION

Children become ill quite often, mainly because of infections which can be managed in the community in most cases. Children are often prescribed antibiotics (AB) unnecessarily,1 which contributes to antimicrobial
resistance, reinforces health-seeking behaviour and unnecessarily increases costs.2

Ambulatory care is where most AB are prescribed, especially for respiratory infections. Children are at particularly high-risk for unnecessary AB prescribing (up to 37%).14 and up to one in four children receives at least one AB prescription/year from their general practitioner (GP).5 6

The care for acutely ill children has traditionally been an ambulatory care responsibility,7 but increasing numbers are seen in hospital. There has been a 40% increase in the number of children presenting to the emergency department (UK) over the last two decades (14% with febrile illness),8 with urgent hospital admission rates up to 25%, mostly for acute infections, which could be managed in the community.9–11

In contrast, serious infections have become rare (<1% of childhood infections).12 Pneumonia represents four-fifth of all cases,13 14 followed by urinary tract infections, and very few cases of sepsis or meningitis,15 in which prompt recognition is essential to avoid complications or death.16 However, the clinical presentation in ambulatory care is highly non-specific, especially in the early stages of illness.

Clinicians often cite diagnostic uncertainty as a reason to prescribe AB.17 Diagnostic uncertainty leads to inappropriate care escalation for patients with non-serious infections, and is a major driver for unplanned hospital admissions,18 which add further pressure to already stretched healthcare services; in Belgium, medical hospital admissions are increasing by 1% per year.19

Only one clinical decision tree for diagnosing serious infections in children has been developed (in 3981 children) and externally validated (in 3142 children) for primary care, with 100% sensitivity and 81% specificity.15–20 The decision tree is considered positive if any of three features is present: clinician gut feeling, dyspnoea and body temperature ≥40°C. The rule achieves a safe and complete rule-out of serious infections but still leaves one in five children in whom uncertainty remains.

Introducing better diagnostic tests might strengthen the ambulatory care management of acutely ill children. Inflammatory markers such as C reactive protein (CRP) and procalcitonin can assist in diagnosing serious infections in hospital settings.21 Up until recently, such blood tests play only a relatively marginal role in ambulatory care because the test result comes back from the laboratory too late to influence clinical decision-making.13

In an international survey, primary care doctors identified infections as a key area for diagnostic innovation, in particular for point-of-care (POC) tests.22

POC platforms that test CRP within 4 minutes (using a finger prick test) have now become available,23 24 and have been introduced in primary care by several companies developing high-standard POC devices.25

As previously established, POC CRP testing should be restricted to children at higher risk after clinical assessment with the decision tree and a CRP threshold <5 mg/L ruling out serious infection with 100% certainty in another 10% of the population, potentially avoiding unnecessary hospital referrals or additional testing.14 This further empowers clinicians to safely manage children in ambulatory care, identifying children with a serious infection without swamping secondary care services.25 26

POC CRP testing may also reduce AB prescribing to acutely ill children in ambulatory care.1 A relatively recent review of the literature showed that using CRP as a POC test reduces AB prescriptions in children if guidance is provided. AB prescriptions by primary care physicians decrease (up to 44%) only if clear instructions on how to interpret the result of the CRP test are provided.27 28

However, these instructions are based either on evidence from studies performed on adult patients or on expert opinion, which could result in inappropriate prescribing in children.

This is further exemplified by a study on POC CRP where parents and clinicians expressed general support for the test, but the doctors wanted specific guidance on how to deal with the test result.29

These previous studies now provide concrete evidence for children-specific thresholds, safe for ruling out serious infections and fit for guiding AB prescribing.

In the ARON trial, practices recruiting children (aged 6 months to 12 years) will be randomized to either (1) a diagnostic algorithm with CRP testing and specific guidance on when to prescribe AB or (2) usual care.

We aim to strengthen the assessment of acutely ill children in ambulatory care, by introducing a diagnostic algorithm that can potentially decrease AB overprescribing and other unnecessary healthcare usage, without affecting patient outcomes.

METHODS AND ANALYSIS

Objectives

The ARON trial will assess whether a diagnostic algorithm, including a standardised clinical assessment, a POC CRP test, and safety-netting advice safely reduce AB prescribing in acutely ill children aged 6 months to 12 years presenting to ambulatory care.

The primary outcome is AB prescribing rate at index consultation (immediate or delayed).

Any reduction in the use of AB should be considered alongside any negative effect. Therefore, secondary outcomes will be considered alongside any potential reduction in AB use, including clinical recovery, consultation and AB prescribing rate during follow-up (day 1 to day 30), and additional investigations (X-Ray, blood tests, urine tests, etc) at index consultation and/or during follow-up (day 1 to day 30).

Exploratory endpoints include mortality at index consultation and/or during follow-up (day 1 to day 30), full clinical recovery at day 7 and day 30, patient’s and physician’s satisfaction (as part of the nested qualitative study), cost-effectiveness of the intervention, adherence...
to the diagnostic algorithm and actual intake of AB (from day 0 to day 30).

In addition, we will describe how the intervention has worked in practice and how clinicians/parents have experienced these consultations as part of a process evaluation (through semistructured interviews).

Design
This study is a multicentre pragmatic cluster-randomized controlled superiority trial.

As the majority of acutely ill children are seen out of hospital by GPs and community paediatricians, the study will be conducted in 122 primary care or community paediatric practices throughout Belgium. The participating practices will be recruited by the academic centres for Primary Care of the KU Leuven, UGent, UAntwerpen, ULiège, UCL and VUB (Brussels).

Eligibility criteria
Practices’ eligibility (and physicians within these practices) for inclusion in the study will be based on the following criteria: being able to recruit acutely ill children (ideally consecutively) and agreeing to the terms of the clinical study agreement.

Practices will be excluded from study participation if they are currently using a POC CRP device as part of their routine care.

Patients’ eligibility for inclusion in the study will be based on the following criteria: children aged 6 months to 12 years, provided informed consent can be obtained, presenting with an acute illness episode that started maximum 10 days before the index consultation. Patients will be excluded from study participation based on the following criteria: previously inclusion in this trial, underlying known chronic condition (eg, asthma, immune deficiency), clinically unstable warranting immediate care, immunosuppressant medication taken in the previous 30 days, trauma as the main presenting problem, AB taken in the previous 7 days, or unwillingness or inability to provide informed consent.

Randomisation
To avoid bias due to physicians working in the same practice randomisation will happen at the level of the practice.

General and community paediatric practices will be randomized in one of the two study arms in a 1:1 ratio using a block randomisation system stratified by recruiting academic region to guarantee that allocation to either usual care or the intervention arm is balanced within every region. Stratified block randomisation will be done using an electronic random numbers generator in blocks of four practices. Randomisation and concealment will be centralised at KU Leuven and conducted by a staff member not involved in data collection or delivering the intervention.

(Un)blinding
Owing to study procedures, children, their parents and physicians will not be masked to the practices’ random allocation and data collection. Conditions and procedures for unblinding are not required as the participating physicians will be aware of their allocation.

Recruitment
Given the current special circumstances under the COVID-19 pandemic, we aim to recruit practices during two stages, with stage 1 acting as a run-in period before all practices will be asked to start recruiting patients. The first stage will allow the study team to recruit a smaller number of practices in a selection of the participating academic centres to further streamline the recruitment process and remedy any unforeseeable issues that might occur after the investigator meeting and study initiation. In a second stage, more practices will be recruited both at the initial academic centres as well as the other participating academic centres. We aim to keep recruitment of practices as pragmatic as possible to limit the burden on practices dealing with the aftermath of the COVID-19 pandemic.

A website with information about the trial will help the recruitment process. The website will contain a form, which can be completed by GPs. Both solo general practices and group practices are eligible for participation in the trial. Per general practice ideally only one or two physicians will be selected for participation in the study, in order not to dilute the number of patients per physician and thus to minimise the possibility of a strong selection of patients towards the most motivated.

Patient identification
The participating physicians will be asked to consecutively recruit children with an acute illness over the recruitment period covering two winter seasons.

Parents and children will be informed about the study by the physician. For that purpose, a patient information leaflet will be developed describing the aim and course of the trial and emphasising the fact that it does allow the physician to overrule the clinical algorithm but aims to investigate whether the intervention may help reduce the AB prescribing rate.

Parents and children willing to participate in the study will be asked to sign an informed consent form (online supplemental material file 1). Consent will be signed by the parents or legal guardian. We will include an age-adjusted assent procedure for older children (≥6 years). The physician will assess eligibility and willingness to participate in the study. No additional procedures are required.

Some practices will be selected based on purposive sampling to take part in the nested qualitative study and will be provided with an additional sheet for the informed consent form to request permission from parents to be contacted by telephone (by a trained qualitative researcher of the study team) during follow-up to take part in a semistructured interview.

Trial assessments
At study entry, the baseline data such as age and gender will be collected for each participating child. Data will
be collected by the physician at the index consultation and entered in the electronic case report form (eCRF) (figure 1).

During the first consultation at baseline, a selection of clinical features will be assessed and recorded by the physician in the patient's health record and on the eCRF, including the features of the clinical decision tree (clinician's gut feeling, body temperature, dyspnoea).

The physician will be asked to note in the patient's health record and on the eCRF whether AB were prescribed, whether this was an immediate or delayed prescription. If the decision to prescribe AB diverged from the suggested algorithm in the intervention arm, physicians will be asked to acknowledge this and explain why on the eCRF. Any additional care during follow-up will be left at the discretion of the child's physician.

Follow-up information for all children will be collected using direct patient/parent contact using a smartphone app. The smartphone app will ask parents and/or children about daily symptoms such as body temperature, treatment and whether they consulted a physician or went to the hospital. Parents will be asked to complete these questions once a day until the symptoms have resolved, and the child is considered cured of the acute illness.

Furthermore, the app will ask parents to complete a few quality-of-life items (proxy version of the EQ-5D-Y questionnaire) and two pain scales (Wong Baker FACES Pain Scale, Face, Legs, Activity, Cry, Consolability (FLACC) scale) during follow-up.

Follow-up information for all children will be collected from the patient's health record up to 30 days after the index consultation. Follow-up information will consist of: diagnosis of a serious infection, reconsultation, medication prescribed, use of additional tests, admission to hospital, death.

A process evaluation will be nested within the pragmatic clustered randomized trial. It will explain how physicians and patients experience the intervention. We aim to identify factors within each arm which influence the management decision to prescribe AB treatment while taking part in the intervention arm or while receiving usual care to build a framework describing the mechanisms required for successful implementation.

The aim of the interviews with clinicians is to explore the experiences of using the diagnostic algorithm (CRP test, safety-netting) to support prudent AB prescribing for acute respiratory tract infections in children among clinicians working in primary care settings. We aim to explore how clinicians use the interventions in their daily practice and how it influences their management decisions and intended future use. The aim of the parent interviews is to explore parents' experiences of consulting a GP participating in the ARON trial, how the diagnostics impact consultations including parent satisfaction and intention to consult in future for similar symptoms.

Individual telephone interviews will be carried out to capture perceived barriers and facilitators to using the diagnostic algorithm including POC CRP testing approach or with the usual care approach.

Physicians (approximately 16) will be purposively sampled to obtain variation in gender, practice setting and experience. Parents (approximately 14–18) will be purposively sampled to obtain variation in age, age and the number of children, sociodemographic background, gender and whether they received AB. Interviews will follow semistructured topic guides exploring physicians' and parents' views and experiences of taking part in the trial. Interviews will be carried out by telephone and analysed using thematic and framework analysis.

**Usual care**

In the control arm, patients will receive ‘usual care’ left at the discretion of the treating physician (figure 2). Apart from the general training session for all participating physicians they have attended prior to recruitment and randomisation, physicians in the control arm will not receive additional tools.

They are expected (but not forced) to follow the Belgian guidelines (as described in Belgian Commission for the Coordination of the Antibiotic Policy National guidelines and the National Institute for Health and Disability
Insurance (RIZIV) consensus meeting ‘Rational use of antibiotics in children’) (figure 3).

**Intervention: diagnostic algorithm**

Guidance will be part of a diagnostic algorithm which includes clinically guided POC CRP testing and safety-netting advice to inform parents on what to expect and what to look out for. CRP testing will be conducted as per the diagnostic algorithm (see figure 4). We will use a POC CRP test which requires 1.5 μL of capillary blood obtained by finger prick (results within 4 min).23 24 Clinical features will be recorded before the CRP test is conducted.

The safety-netting advice will be supported by a parent information booklet, based on previous research (the ‘When should I worry’-interactive booklet (a guide to Coughs, Colds, Earache & Sore Throats),33 the ‘Mijn kind heeft koorts’ booklet (Eefje de Bont, www.thuisarts.nl)34 and the ‘Caring for children with coughs’-leaflet (information about how to look after a child who has a cough and when to see the doctor)).35

Patient recruitment started on 24 February 2021 and is expected to last until 1 December 2022.

**Statistics and data analysis**

The main aim of our study is to establish the assumed superiority of a diagnostic algorithm including a standardised clinical assessment, a POC CRP test, and safety-netting advice over usual care to reduce AB prescribing rates.

Previous research in a similar population has shown approximately 17% of children testing positive if yes to any of three features: clinician gut feeling, dyspnoea and body temperature ≥40 °C.15 In all children, 30.43% will be prescribed AB.28

If a diagnostic algorithm including the clinical decision tree, POC CRP test and safety-netting advice is provided, based on the abovementioned information and after consulting the key stakeholder groups (eg, patients, physicians and healthcare funder), we can prudently assume to expect the AB prescribing rate in all children to be reduced to 22.65% in the intervention arm, based on our systematic review,36 the previous trials in acutely ill children14 37 and a previous systematic review in adults.38

Considering the required sample size for these analyses of the primary study outcome and the secondary outcomes, aiming to recruit a total sample size of 6111 patients will be sufficient (online supplemental material file 2).

The planned recruitment period will be 21 months, starting 24 February 2021. Considering an inclusion rate of 1 in 5 of all eligible children, we will include a total of 122 ambulatory care physicians.

Presentation of baseline characteristics of the study population and comparability of the two arms will be based on the following variables: age (median and 25–75 percentiles) and gender (percentage).

Differences in baseline characteristics and clinical features will be analysed through $\chi^2$ testing and non-parametric equality-of-medians testing to assess potential recruitment bias.

The primary and secondary endpoints will be analysed according to the intent-to-treat approach.
We will use a mixed-effects logistic regression analysis to account for the clustering at practice level.

Multiple imputation will be applied to deal with missing data. Imputation will be performed for the binary outcome variable and logistic regression will be used as imputation model. Predictors for the imputation model are baseline patient characteristics and intervention.

Subgroup analysis will be performed to investigate how the primary outcome behaves in function of age categories and gender.

**Cost effectiveness**

First, we will perform a cost study aiming to calculate total costs of the intervention, to identify significant cost drivers and to compare the cost impact of the intervention with its alternative usual care. The potential subcategories of costs considered are: acute outpatient, acute inpatient, ambulatory care, residential care, pharmacy prescriptions, chronic prescriptions, diagnostic tests, visit to the emergency department, intervention costs.39 Predominantly, a healthcare payer perspective will be adopted, which includes payments out of the Belgian government’s and the communities’ healthcare budget as well as patients’ copayments for healthcare consumption, hence excluding productivity or other indirect costs (online supplemental material file 3).

The second part is a cost–consequences analysis, comparing costs with various consequences (expressed in reductions in hospitalisations, consultations, pharmaceuticals (reimbursed and non-reimbursed)) and a cost–utility analysis using broader outcome metrics such as quality-adjusted life years (QALYs), to express the differences in health outcomes between participants intervention group and those in the usual care group.

For both study groups, resource use data and health-related quality of life (HRQOL) data will be collected during the trial using information from the patients’ health records and using a questionnaire (self-reported) as part of the smartphone app for parents for those resources not captured by the health records. Simultaneously, information from the RIZIV nomenclature...
A database will be used to attach costs to the different resource use data. Alongside the data collected from the app during the trial, the costs associated with hospitalisation, consultations, pharmaceuticals (reimbursed) during follow-up will be collected by linking the national insurance number (collected during the index consultation by the participating physician) of children via a trusted third party to the administrative databases reporting on healthcare usage. The HRQOL data will be collected using the proxy version of the EQ-5D-Y questionnaire (filled out at regular timings by the participants (by parents)). As we anticipate a large proportion of our study population to be below the age of 4 years, we will include additional scales aiming to assess quality of life or rather pain as this is assumed to be the main driver for quality of life in the young infants and has shown to have face validity:

- The Wong Baker FACES Pain Scale, which has been validated in children from 3 years to 18 years of age.
- The FLACC scale, which has been validated in children from 0 to 18 years of age.

Resource use data will be collected during follow-up by linking the national insurance number to the administrative healthcare usage databases, as well as from the data collected in the parental app (hospitalisation, consultation, etc). This complementary approach is preferred to avoid missing data and assess representativeness of our analysis.

Information related to the intervention costs (equipment, training, etc) will be collected, including the physician’s time spent on the programme (as reported by the participating physicians in the nested qualitative study). The latter costs will be recalculated at patient level.

We will calculate incremental cost-effectiveness ratios in terms of costs incurred for natural effects avoided (hospitalisations, consultations, number of packages AB reimbursed) and incremental cost–utility ratios in terms of costs-per-QALY-gained, or net benefits (in case of dominated or dominant interventions).

Decision-analytic modelling will be used to predict longer term outcomes and complications for cohorts of patients as well as their expected economic impact, as well as to investigate the effect of changes in particular parameters (through scenario and sensitivity analyses).

Health economic evaluation studies are frequently characterised by degrees of uncertainty or methodological considerations. In the current study, one-way, multiway and probabilistic (Monte Carlo/non-parametric bootstrapping) sensitivity analyses will be conducted to handle various uncertainties. Uncertainty analyses will be expressed in terms of cost-effectiveness acceptability curves.
Data handling

Study data will be collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at KU Leuven. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Data monitoring

The investigator will permit trial-related monitoring, and audits, providing direct access to all related documents. eCRFs, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor’s clinical trial monitor and auditor. The accuracy of the data will be verified by review of these documents.

For all details about monitoring, we refer to the Trial Monitoring Plan (see online supplemental appendix), which will be developed and agreed by the Trial Management Group and Trial Steering Committee based on the trial risk assessment.

Public and patient involvement

We will present the suggested intervention to parents and children to receive input on potential barriers and facilitators of our proposed trial. Furthermore, patient representative groups will be contacted to obtain useful feedback regarding our trial.

ETHICS AND DISSEMINATION

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements. Approval of this protocol, the informed consent forms and other related documents, for example, advertisements and physician information letters, was obtained on 10 November 2020 from the Ethics Committee Research of University Hospitals Leuven under reference S62005. Parents/guardians provided informed consent for participants aged under 18.

We will ensure that the findings of the study will be disseminated to relevant stakeholders other than the scientific world including the public, healthcare providers and policy makers. In case this study proves our diagnostic algorithm to be more effective than usual care to reduce AB prescribing rate in children, translating this evidence into routine practice will be the next great challenge.

The process evaluation that is part of this trial will be informative in respect to this and hence provide a basis for an implementation strategy. It will be essential to educate physicians about introducing the diagnostic algorithm including POC CRP testing and safety-netting advice in their daily practice. This will require training which should be delivered through accredited Continued Medical Education but should also be part of the basic medical curriculum for physicians. The engagement of most of the Belgian academic centres for general practice in this trial will undoubtedly facilitate the integration of education about diagnosis and management of infectious diseases in children in ambulatory care—in combination with AB prescribing guidelines—in the medical curriculum.

ETHICS STATEMENTS

Ethics approval for this study was obtained on 10 November 2020 from the Ethics Committee Research of University Hospitals Leuven under reference S62005 (online supplemental material file 5). Parents/guardians provided informed consent for participants aged under 18.

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Contributors

The study sponsor and funder had no role in study design, set up of the trial, writing of the report, and the decision to submit the report for publication. For detailed information regarding the composition, roles, and responsibilities of the coordinating centre, steering committee, data monitoring team, and data management team, please see the full ARON trial protocol (online supplemental material file 4). The study was conceived by JYJV, AVDB, SC, SA, JL and ADS. AL was involved in drafting the statistical analysis. JYJV prepared the first draft of the manuscript. All authors commented on subsequent drafts of the protocol and approved the final version.

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Competing interests

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Supplemental material

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REFERENCES

1. Little P, Francis NA, Stuart B, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial. Lancet 2021;398:1417–26.

2. O’Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on antimicrobial resistance. 2014. Available: https://antimicrobial-resistance.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20danger%20for%20human%20health%20and%20wealth%20of%20nations_1.pdf

3. Ashdown HF, Räsänen U, Wang K, et al. Prescribing antibiotics to ‘at-risk’ children with influenza-like illness in primary care: qualitative study. BMJ Open 2016;6:e011497.

4. Elshout G, van Ierland Y, Bohnen AM, et al. Alarm signs and antibiotic prescription in febrile children in primary care: an observational cohort study. BMJ Pract 2013;63:e437–44.

5. de Boett EGM, van Loo IHM, Dukers-Muijers NHTM, et al. Oral and topical antibiotic prescriptions for children in general practice. Arch Dis Child 2013;98:228–31.

6. Elshout G, Kool M, Van der Wouden JC, et al. Antibiotic prescription in febrile children: a cohort study during out-of-hours primary care. J Am Board Fam Med 2012;25:810–8.

7. Fleming DM, Smith GE, Charlton JRH, et al. Impact of infections on primary care: greater than expected. Commun Dis Public Health 2002;5:7–12.

8. Sands R, Shanmugavadivel D, Stephenson T, et al. Medical problems presenting to paediatric emergency departments: 10 years on. Emerg Med J 2012;29:379–82.

9. Gill PJ, Goldacre MJ, Mant D, et al. Increase in emergency admissions to hospital for children aged under 15 in England, 1999–2010: national database analysis. Arch Dis Child 2013;98:328–34.

10. Purdy S, Griffin T, Salisbury C, et al. Ambulatory care sensitive conditions: terminology and disease coding need to be more specific to aid policy makers and clinicians. Public Health 2009;123:169–73.

11. Borensztajn DM, Hagedorn NN, Rivero Calle I, et al. Variation in hospital admission rates for febrile children evaluated at the emergency department (ED) in Europe: perform, a multicentre prospective observational study. PLoS One 2021;16:e0244810.

12. Van den Brue J, Bartholomeeusen S, Aertgeerts B, et al. Serious infections in children: an incidence study in family practice. BMC Fam Pract 2006;7:23.

13. Van den Brue J, Thompson M. Research into practice: acutely ill children. Br JGen Pract 2014;64:311–3.

14. Verbakel JY, Lemienre MB, De Burghgraave T, et al. Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial. BMC Med 2016;14:131.

15. Verbakel JY, Lemienre MB, De Burghgraave T, et al. Validating a decision tree for serious infection: diagnostic accuracy in acutely ill children in ambulatory care. BMJ Open 2015;5:e008657.

16. Van den Brue J, Haji-Hassan T, Thompson M, et al. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. Lancet 2010;375:834–45.

17. Wang D, Liu C, Zhang X, et al. Does diagnostic uncertainty increase antibiotic prescribing in primary care? NPJ Prim Care Respir Med 2021;31:17.

18. Saxena S, Bottle A, Gilbert R, et al. Increasing short-stay unplanned hospital admissions among children in England; time trends analysis 97–06. PLoS One 2009;4:e7484.

19. Afdeling Informatie en Zorg Vooroplen: Statistiek van de doodsoorzaaken. Agentschap Zorg en Gezondheid. 2012. Available: http://www.zorg-en-gezondheid.be/cijfers/ [Accessed 6 Jan 2018].

20. Van den Brue J, Aertgeerts B, Bruyninckx R, et al. Signs and symptoms for diagnosis of serious infections in children: a prospective study in primary care. Br J Gen Pract 2007;57:538–46.

21. Van den Brue J, Thompson MJ, Haji-Hassan T, et al. Diagnostic value of laboratory tests in identifying acutely ill children in primary care: systematic review. BMJ 2011;342:d3082.

22. Howick J, Cals JWl, Jones 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:e000651.

23. Minnaard MC, van de Pol AC, Broekhuizen BDL, et al. Analytical performance, agreement and user-friendliness of five C-reactive protein point-of-care tests. Scand J Clin Lab Invest 2013;73:627–34.

24. Verbakel JY, Aertgeerts B, Lemienre M, et al. Analytical accuracy and user-friendliness of the Alinon point-of-care CRP test. J Clin Pathol 2014;67:83–8.

25. Future Hospital Commission. Future hospital: caring for medical patients. London: Royal College of Physicians, 2013.

26. Maruthappu M, Sood HS, Keogh B. The NHS five year forward view: implications for clinicians. BMJ 2014;349:g6518.

27. Do NT, Ta NTD, Tran NTH, et al. Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary care health: a randomised controlled trial. Lancet Glob Health 2016;4:e633–41.

28. Lemienre MB, Verbakel JY, Colman R, et al. Point-of-care CRP matters: normative CRP levels reduce immediate antibiotic prescribing for acutely ill children in primary care: a cluster randomized controlled trial. Scand J Prim Health Care 2018;36:423–36.

29. Van den Brue J, Jones C, Thompson M, et al. C-reactive protein point-of-care testing in acutely ill children: a mixed methods study in primary care. Arch Dis Child 2016;101:382–6.

30. Kreimeier S, Greiner W. EQ-5D-Y as a health-related quality of life instrument for children and adolescents: the instrument’s characteristics, development, current use, and challenges of developing its values. J Health Med 2019;22:31–7.

31. Lawson SL, Hogg MM, Moore CG. Pediatric pain assessment in the emergency department: patient and caregiver agreement using the Wong-baker faces and the faces pain scale revised. Pediatr Emerg Care 2019.

32. Manworren RB, Hynan LS, Clinical validation of FLACC; preverbal patient pain scale. Pediatr Nurs 2003;29:140–6.

33. Thompson M, Vodicka TA, Blair PS, et al. Duration of symptoms of respiratory tract infections in children: systematic review. BMJ 2013;347:f7027.

34. de Boett EGM, Dinant G-J, Elshout G, et al. Booklet for childhood fever in out-of-hours primary care: a cluster-randomized controlled trial. Fam Ann Med 2018;16:314–21.

35. Hay AD, Redmond NM, Turnbull S, et al. Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and acute cough: a prognostic cohort study. Lancet Respir Med 2016;4:902–10.

36. Verbakel JY, Lee JJ, Goyder C, et al. Impact of point-of-care C-reactive protein in ambulatory care: a systematic review and meta-analysis. BMJ Open 2019;9:bmjopen-2018-025036.

37. Schot MJ, Van den Brue A, Broekhuizen BD, et al. Point-of-care C-reactive protein to assist in primary care management of children with suspected non-serious lower respiratory tract infection: a randomised controlled trial. BJGP Open 2018;2:bjgopen18X10160.

38. Aabenhuis R, Jensen JU, Jørgensen KJ. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev 2014;11:CD010130.

39. Carreras M, Sánchez-Pérez I, Ibern P, et al. Analysing the costs of integrated care: a case on model selection for chronic care purposes. Int J Integr Care 2016;16:10.

40. Stinson JN, Kavanagh T, Yamada J, et al. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. Pain 2006;125:143–57.

41. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain 2007;127:140–50.

42. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.

43. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.