A clinical decision tool including a decision tree, point-of-care testing of CRP, and safety-netting advice to guide antibiotic prescribing in acutely ill children in primary care in Belgium (ARON): a pragmatic, cluster-randomised, controlled trial

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Summary

Background Antimicrobial resistance is a global health threat. Many children with acute illness in ambulatory care are unnecessarily prescribed antibiotics. We assessed the clinical effectiveness of a clinical decision tool for these children, including a validated decision tree, guided point-of-care C-reactive protein testing (POCT of CRP), and safety-netting advice.

Methods ARON was a multicentre, unblinded, pragmatic, cluster-randomised, controlled trial conducted at eligibile Belgian general practitioner and community paediatrician practices able to recruit children with acute illness consecutively, and not already doing POCT of CRP. Practices were allocated (1:1) with equal size (n=4) block randomisation to the clinical decision tool or usual care, stratified by recruiting academic centre. Children with acute illness aged 6 months to 12 years were recruited and followed up for 30 days. The coprimary outcomes were antibiotic prescribing at the index consultation (tested for superiority), as well as recovery time, additional testing, follow-up visits, and antibiotic prescribing after index consultation (all tested for non-inferiority with margins of 1 day, 3%, 4%, and 2%, respectively). Coprimary outcomes were analysed with logistic regression, accounting for practice clustering, study arm, and age in the intention-to-treat population, except recovery time, which was analysed with Cox regression adjusting for the same covariates. Safety was assessed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov (NCT04470518) and is completed.

Findings Of 171 eligible practices, we randomly allocated 82 to the intervention group and 89 to the usual care group. Between Feb 24, 2021, and Dec 29, 2023, 7049 participants were screened, of whom 6760 were deemed eligible. Five patients in each study arm were excluded, so we analysed data from 6750 participants (2988 in the intervention group and 3762 in the control group; 3447 [51%] boys, 3302 [49%] girls, one [<1%] did not specify). The intervention significantly reduced antibiotic prescribing at the index consultation (466 [16%] *vs* 817 [22%], adjusted odds ratio 0·72 [95% CI 0·55–0·94]; p=0·017). Recovery time (adjusted mean difference –0·1 day [95% CI –0·5 to 0·3]), additional testing (adjusted absolute risk reduction [aARR] 2·0% [–1·7 to 5·0]), follow-up visits (aARR 2·8% [–0·9 to 6·1]), and antibiotic prescribing after index consultation (aARR 2·4% [0·2 to 4·2]) were all non-inferior in the intervention group versus the control group. 90 (88%) of 102 adverse events were serious (30 [1%] in the intervention group and 60 [2%] in the control group); none were deemed related to the study procedures. No child died throughout the trial.

Interpretation The clinical decision tool reduced antibiotic prescribing in children without causing harm. Our results support its broader dissemination and implementation to improve the management of acutely ill children in ambulatory care.

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Introduction

In 2019, bacterial antimicrobial resistance was linked to 4·95 million deaths globally, including 604 000 in high-income countries.[1] Antimicrobial resistance ranks among the top global health threats, driving up health-care costs, treatment failures, and mortality.[2] In 2020, over 800 000 antibiotic-resistant infections in the European Economic Area caused over 35 000 deaths, a burden similar to influenza, tuberculosis, and HIV combined.[3] Antibiotic use is a major driver of antimicrobial resistance.[2] Children are at particularly high risk of unnecessary antibiotic prescribing,[4] with about 86% of

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Research in context

Evidence before this study

In 2019, approximately 604 000 deaths were associated with antimicrobial resistance in high-income countries alone, with 141 000 directly attributable to antimicrobial resistance. The European Centre for Disease Prevention and Control (ECDC) reports that over 800 000 infections caused by antibiotic-resistant bacteria occurred in the European Economic Area in 2020, resulting in more than 35 000 deaths directly linked to these infections, similar to the health burden of influenza, tuberculosis, and HIV combined. The 2022 WHO and ECDC report on antimicrobial resistance surveillance in Europe states that antimicrobial resistance remains a health threat in Europe and that robust investments in interventions to address antimicrobial resistance are urgently needed and would substantially positively impact population health and future health-care expenditures. The strong relationship between antibiotic consumption in the community and the proliferation of antimicrobial resistance has been established, and children are at particularly high risk of unwarranted antibiotic prescribing. We systematically searched Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Database of Abstracts of Reviews of Effects, and Science Citation Index for controlled studies published in all languages from database inception to March 21, 2017, assessing the impact of point-of-care testing (POCT) of C-reactive protein (CRP) on clinical care for adults and children in ambulatory settings. The search terms are listed in the appendix (pp 3–5). All 19 included studies had a high risk of performance and selection bias. POCT of CRP significantly reduced immediate antibiotic prescribing in children only when guidance on antibiotic prescribing relative to CRP concentrations was provided. No significant effect was found on patient satisfaction, clinical recovery, follow-up visits, further testing, or hospital admission. These results were supported by a 2022 Cochrane systematic review update, which found that POCT of CRP likely reduces antibiotic prescribing for respiratory tract infections (RTIs) in children, from 51% to 37%. The authors recommend additional research on children, including establishing CRP cutoff values for withholding antibiotics and validating CRP decision algorithms. Two recent UK-based cluster-randomised controlled trials showed no evidence that multifaceted interventions could reduce antibiotic prescribing rates for children with RTIs presenting to primary care. However, these interventions were not first externally validated. Qualitative research revealed that interventions aimed at reducing unnecessary antibiotic prescriptions for children with RTIs should focus on boosting clinicians' confidence in the safety of withholding prescriptions. Likewise, interventions to decrease consultations for RTIs should work on enhancing parents' confidence in their ability to discern between self-limiting illnesses and those that might require medical management, treatment, or both.

Added value of this study

By addressing these issues, the ARON trial showed that a multifaceted clinical decision tool consisting of a validated decision tree, guided POCT of CRP, and safety-netting advice can safely reduce antibiotic prescribing for acutely ill children in primary care. Importantly, this reduction in antibiotic prescribing is not associated with worse clinical outcomes in terms of illness duration, additional testing, number of follow-up visits, or antibiotic prescribing after the index consultation.

Implications of all the available evidence

Our findings support dissemination of the ARON trial's multifaceted clinical decision tool, which combines an externally validated decision tree, guided interpretation of CRP testing, and safety-netting advice. Unlike earlier studies that examined CRP testing in isolation, this trial shows that integrating these components can safely reduce inappropriate antibiotic prescribing for children with acute illness without without compromising child safety or recovery.

acute otitis media visits in high-income countries leading to an antibiotic prescription.[5] Diagnostic uncertainty, among other factors,[6] contributes to increased antibiotic prescribing, escalating care for non-serious infections and driving antimicrobial resistance and unplanned hospital admissions.[7] Serious infections (defined as sepsis, meningitis or encephalitis, pneumonia, complicated urinary tract infection, infections of the musculoskeletal system, cellulitis, infection of the circulatory system, severe gastrointestinal infection or dysentery, and other diagnoses such as whooping cough) occurred in approximately 5% of infections in children aged 0–12 years, with pneumonia accounting for 17 children per 1000 person-years in Flanders, Belgium, in 2022.[8] No single clinical feature can rule out those serious childhood infections that eventually require hospitalisation, but a combination of features can.[9] Only one clinical decision tree for diagnosing such infections has been developed and validated for primary care, with 100% (95% CI 72–100) sensitivity and 84% (82–85) specificity.[10,11] This decision tree is positive if any of three features are present: a gut feeling by the physician that things were not right, current dyspnoea, or current or recent body temperature of 40°C or higher (parent-reported or patient-reported). Better diagnostic tests, particularly in point-of-care testing (POCT), could improve the management of acutely ill children in ambulatory care, with infections identified as a key area for innovation.[12] POCT platforms that test C-reactive protein (CRP) within 3 min using a fingerprick are available,[13,14] but should be limited to children at high risk identified by the decision tree.[15] In these children, a CRP threshold of less than 5 mg/L can help rule out serious infections, potentially preventing unnecessary referrals

or tests.[15] Our previously published systematic review and meta-analysis showed that the use of POCT of CRP could reduce antibiotic prescriptions by up to 44% in acutely ill children in primary care, but only with clear instructions on interpreting results.[16] Parents and physicians generally support POCT of CRP, but physicians require guidance on interpreting results.[17] Safety-netting advice is essential in consultations for acute paediatric illness,[18] and paper safety-netting advice can safely reduce antibiotic use and return visits.[19]

We aimed to evaluate whether a clinical decision tool, including a validated decision tree, guided POCT of CRP, and safety-netting advice could safely reduce antibiotic prescribing in acutely ill children in ambulatory care.

Methods

Study design

The ARON trial is a multicentre, parallel-group, pragmatic, cluster-randomised, controlled trial conducted in general practitioner and community paediatric practices across Belgium, following a previously published protocol.[20] Practices were the unit of randomisation, and were recruited by six Belgian academic centres for primary care: KU Leuven, Ghent University, University of Antwerp, University of Liège, University of Louvain, and Free University of Brussels.

The trial adheres to the CONSORT checklists for cluster-randomised trials and pragmatic trials (appendix pp 6–11),[21,22] and we obtained ethics approval on Nov 10, 2020, from the Ethics Committee Research of University Hospitals Leuven (S62005) and all participating academic centres. The trial was registered with ClinicalTrials.gov (NCT04470518).

Participants

Practices were eligible if they were a Belgian general practitioner or community paediatric practice able to recruit children with acute illness consecutively. Practices already using POCT of CRP devices were excluded due to possible preconceptions about its clinical use.

Recruitment involved engaging practices in our clinical research network, sending invitations through local medical associations (eg, Domus Medica), newsletters of the academic centre of KU Leuven and the Belgian Association for Paediatrics, promoting the study on our website, and directly contacting practices by telephone.

Eligible patients were children aged 6 months to 12 years with an acute illness episode within 10 days before the consultation, with a parent or legal guardian able to provide informed consent. Exclusion criteria included previous trial participation, chronic conditions (eg, asthma, immune deficiency), clinical instability requiring immediate care, immunosuppressant use in the previous 30 days, trauma as the main issue, or antibiotic use in the previous 7 days. Gender was self-reported by the parent or the child if they felt confident expressing their gender identity, with the options: male, female, X (ie, neither male nor female), or prefer not to say.

Randomisation and masking

Practices were randomised 1:1 into two study arms (to provide usual care or POCT of CRP) with block randomisation, stratified by recruiting academic centre, with an electronic random-number generator assigning blocks of four. Randomisation and concealment were centralised at the sponsor (KU Leuven, Leuven, Belgium) and conducted by a staff member uninvolved in intervention delivery or data collection. JYV generated the random sequence, TDB assigned clusters to the trial groups, and physicians enrolled participants. Due to the nature of the trial, participants, physicians, outcome assessors, and data analysts were not masked to random allocation and data collection.

Procedures

Before recruitment and randomisation, physicians in both groups attended a training session covering the rationale, objectives, and practicalities of the study, and best practices for paediatric antibiotic prescribing as outlined by the Belgian Antibiotic Policy Coordination Committee and the National Institute for Health and Disability Insurance consensus meeting on the rational use of antibiotics in children (appendix p 12).[23]

See Online for appendix

After randomisation, the usual care group managed patients per their normal procedures. The intervention group received the clinical decision tool (appendix p 13), but could overrule it based on clinical judgement, documenting the reason. They were provided with an Afinion 2 Analyzer for POCT of CRP (Abbott, Princeton, NJ, USA), rented by the sponsor, with CRP cartridges (Abbott) and paediatric lancets (Sarstedt, Nümbrecht Germany), supplied by the sponsor. Physicians were trained onsite by their study coordinator to perform POCT of CRP with 1·5 µL of capillary blood from a fingerprick (results within 3 min).

The safety-netting advice booklet, designed for this trial and based on previous research, aimed to inform parents about the natural course of the illness and highlight red flags indicating the need for medical care (appendix pp 14–19).[20]

Physicians recorded all procedures in the electronic health record and in an electronic case report form (eCRF) via Research Electronic Data Capture (REDCap; version 10.0.30), hosted at KU Leuven. During the initial consultation, they screened participants and obtained written consent and optional age-adjusted assent for children aged 6 years or older. Baseline data, provided by parents, included the child's age, gender, illness duration, whether the child's illness differed from previous episodes, and details on fever and any fever medication. Physicians documented clinical data such as illness severity, body temperature on physical examination, weight, and responses to the three decision-tree

questions. Race or ethnicity data were not collected to avoid any potential implications or biases associated with categorising participants by these factors.

Intervention group physicians were guided through the various steps and questions of the clinical decision tool within the eCRF. During this process, they documented whether they were considering prescribing antibiotics, performed POCT of CRP, and noted any repeated attempts due to CRP device errors. Additionally, they recorded the CRP values obtained and, if applicable, provided reasons for deviating from the tool's recommendations. All physicians registered the working diagnosis using classifications from the International Classification of Primary Care, second edition;[24] any secondary diagnoses; antibiotic prescriptions, including type, dose, frequency, duration, and reasons for prescribing; fever medication advice; additional tests; and referrals. In the intervention group, parents received a paper version of the booklet near the end of the consultation when the physician explained the working diagnosis and management plan.

We collected daily follow-up information for all children until symptom resolution (up to 30 days) through patient or parent contact using an electronic patient diary via a smartphone app (appendix p 20). The physician informed the parents about the diary when obtaining informed consent, although completing the diary was not mandatory for participation in the trial. The diary inquired about symptoms (eg, body temperature), treatments, and any physician consultations or hospital visits. Developed in collaboration with an app developer (Zenjoy, Heverlee, Belgium), the usability of the app was assessed and improved with parents and children before recruitment.

Follow-up data for up to 30 days from the index consultation were recorded in the eCRF by the physician or their study coordinator. These data included the final diagnosis, deaths, hospital admissions and referrals, number and location of follow-up visits, additional testing, and the prescription of antibiotics (including reasons) or other prescribed medications. Both serious and non-serious adverse events were recorded. Physicians were required to report any serious adverse events, such as hospitalisations or deaths, within 24 h.

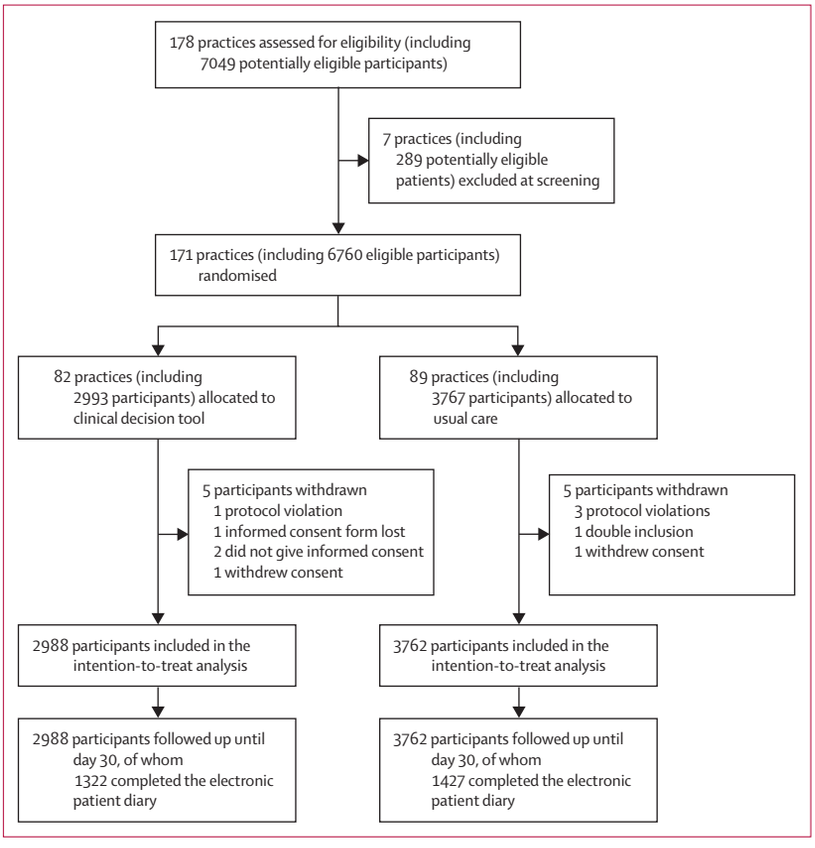

Figure 1: **Trial profile**

Outcomes

Coprimary outcomes, assessed centrally and all analysed at the individual rather than the cluster level, were antibiotic prescriptions at the index consultation (immediate or delayed), time to full clinical recovery, additional investigations (x-rays, blood tests, urine tests, etc) between the index consultation and day 30, follow-up visits, and antibiotic prescriptions after the index consultation. In our protocol and statistical analysis plan, we refer to antibiotic prescriptions at the index consultation as the primary outcome, and the other outcomes listed above as secondary outcomes; however, we report all these outcomes as coprimary outcomes in this Article since the sample size calculation was powered to account for all of them; this reflects the original study design and is not a deviation from the initial protocol.

Exploratory endpoints were categorised by follow-up time. At the index consultation, we assessed the proportion of children receiving additional investigations, hospital referrals or admissions, and adherence to the clinical decision tool. During the follow-up, we reassessed these outcomes, measured the proportion of patients reaching full clinical recovery at days 7 and 30, and evaluated patient and physician satisfaction (reported separately in the nested process evaluation).[25] Mortality was tracked until day 30. Safety was established by assessing the number of adverse events. Full details of all the prespecified outcomes can be found in the protocol.[20] All data were collected from the eCRF, except for time-to-recovery outcomes, which were obtained from the patient diary.

Statistical analysis

We aimed to establish the presumed superiority of the clinical decision tool over usual care for the antibiotic prescribing proportion at index consultation, and its non-inferiority for the other coprimary outcomes (statistical analysis plan available in the appendix

[pp 21–28]). To account for potential negative effects, our study was powered on all coprimary outcomes.[26] Previous research found that 17% of children test positive on the decision tree and 30% are prescribed antibiotics.[11,27] Based on these findings, along with data from other studies and stakeholder consultations, we estimated the intervention would reduce antibiotic prescribing to 23%.[16,28] Non-inferiority margins were 1 day for recovery time, 3% for additional testing, 4% for follow-up visits, and 2% for antibiotic prescribing after the index consultation (appendix p 29). By use of the Bonferroni–Holm correction, the significance levels (α) of these coprimary outcomes were 0·0125, 0·0167, 0·025, and 0·05, respectively.

We initially aimed to recruit 6111 children, including a 10% buffer for non-recruiting practices, with an anticipated antibiotic prescribing rate of 30% in the control group and 23% in the intervention group, an anticipated mean cluster size of 50 patients, an anticipated intraclass correlation coefficient (ICC) of 0·063—all based on previous research in the exact same population[11,27]—and an α of 0·05 and power of 0·90. However, data from the first 4938 children revealed a lower than expected overall prescribing rate of just 18%, reflecting a known consistent decline in paediatric antibiotic prescribing by Flemish general practitioners in previous years, a trend further accelerated by the COVID-19 pandemic.[8] We recalculated the required sample size to 7000, including a 10% buffer, and obtained ethics approval for the protocol amendment on May 4, 2023. For these calculations, we used the same cluster size, ICC, α, and power as before, but an anticipated antibiotic prescribing rate in the control group of 21% and the intervention group of 14%, based on the preliminary findings in the ARON trial at that time.

Baseline characteristics were reported as percentages and medians with IQRs. Binary coprimary outcomes were analysed with a generalised linear mixed-effects model with a logit link (binomial family). Fixed effects included study arm and age, with a random intercept for practice-level clustering. Models were fitted with glmer from the lme4 package in R version 4.2.3 (2023-03-15 ucrt) and RStudio version 2024.4.2.764, assuming an unstructured covariance for the random effect. Results were reported as frequencies, proportions, adjusted odds ratios (aORs), and adjusted absolute risk reduction (aARR) with 95% CIs. aARRs were derived from the aORs by applying the observed control group risk as baseline. We used the oddsratio_to_arr() function from the effectsize package in R to convert aORs and their 95% CIs into adjusted aARRs, expressed in percentage points. For the time-to-event outcome (ie, duration until full clinical recovery), a mixed-effects Cox regression model was used, with a random intercept to account for practice-level clustering. The proportional hazards assumption was assessed through visual inspection of Kaplan–Meier

	Intervention (n=2988)	Control (n=3762)
Age		
Median, years	3·7 (1·6–7·1)	3·9 (1·8–7·2)
Age category		
0·5–1	924 (31%)	1030 (27%)
2–6	1290 (43%)	1729 (46%)
7–12	774 (26%)	1003 (27%)
Gender		
Boy	1566 (52%)	1881 (50%)
Girl	1421 (48%)	1881 (50%)
X	0	0
Prefer not to say	1 (<1%)	0
Medical specialty of recruitment		
General practitioner	2719 (91%)	3459 (92%)
Community-based paediatrician	269 (9%)	303 (8%)
Body temperature on patient history, °C	39·0 (38·5–39·5)	39·0 (38·5–39·5)
Body temperature on physical examination, °C	37·0 (36·5–37·7)	36·9 (36·5–37·5)
Bodyweight, kg	15·3 (10·7–23·0)	16·1 (11·2–24·5)
Illness duration, days	2·5 (1·3–4·0)	2·2 (1·0–4·0)
Illness severity as indicated by the physician during the index consultation		
Mild	1771 (59%)	2449 (65%)
Moderate	1146 (38%)	1238 (33%)
Severe	69 (2%)	75 (2%)
Child's illness deemed different from previous episodes by parents		
Yes	587 (20%)	730 (19%)
No	2397 (80%)	3031 (81%)
Responses to the three decision-tree questions		
Clinician gut feeling that something is wrong		
Yes	275 (9%)	290 (8%)
No	2708 (91%)	3446 (92%)
Dyspnoea		
Yes	80 (3%)	110 (3%)
No	2904 (97%)	3627 (96%)
Highest measured body temperature ≥40°C (history or at examination)		
Yes	218 (7%)	261 (7%)
No	2761 (92%)	3473 (92%)
Illness diagnoses by ICPC-2 code		
R74—acute upper respiratory infection	1084 (36%)	1373 (36%)
H71—acute otitis media or myringitis	298 (10%)	439 (12%)
A77—viral disease other or NOS	232 (8%)	241 (6%)
R78—acute bronchitis or bronchiolitis	219 (7%)	253 (7%)
R76—acute tonsillitis	157 (5%)	198 (5%)
R80—influenza or possible COVID-19	166 (6%)	178 (5%)
D73—gastroenteritis presumed infection	134 (4%)	187 (5%)
D70—gastrointestinal infection	125 (4%)	124 (3%)
R81—pneumonia	71 (2%)	85 (2%)
A03—fever	55 (2%)	64 (2%)
R77—laryngitis, acute tracheitis, or proven COVID-19	68 (2%)	110 (3%)
Other	379 (13%)	510 (14%)
Children with a secondary diagnosis during index consultation	399 (13%)	507 (13%)

Data are n (%) or median (IQR). ICPC-2=International Classification of Primary Care, second edition. NOS=not otherwise specified.

Table 1: **Baseline characteristics**

curves and a formal Schoenfeld residual analysis. Time-to-event outcomes were expressed as means, pooled SDs, adjusted hazard ratios (aHRs), and adjusted mean differences (aMDs) with 95% CIs. All analyses, including the safety analysis, were conducted on an intention-to-treat basis.

Missing data from the electronic patient diaries in the base case were addressed using multiple imputation by chained equations. For comparison, results from complete case analysis and bootstrapping multiple imputation are presented in the appendix (pp 30–34), along with details on missingness and the different imputation methods used. The algorithm for calculating the days until full clinical recovery is detailed in the appendix (p 35).

We performed prespecified subgroup analyses to explore coprimary outcomes by age categories (0–1 years, 2–6 years, and 7–12 years) and gender (boy, girl, X, and prefer not to say). Additionally, we performed prespecified sensitivity analyses. The first, a consecutive inclusions analysis, excluded practices based on one or more of these criteria: (1) fewer than ten children recruited per year, (2) POCT of CRP performed on more than 90% of children, or (3) most children (ie, >90th percentile) scored negative on all decision-tree items. The per-protocol sensitivity analysis included only participants managed according to the protocol, excluding patients for whom

	Intervention (n=2988)	Control (n=3762)	aOR or aHR* (95% CI)	aARR or aMD* (95% CI)	p value
Co-primary endpoints†					
Antibiotic prescribing at the index consultation (immediate or delayed)	466 (16%)	817 (22%)	0·72 (0·55–0·94)	5·1% (1·0 to 8·5)	0·017
Duration until full clinical recovery, days	4·6 (3·5)	4·7 (3·6)	1·03 (0·96–1·09)	–0·1 (–0·5 to 0·3)	NA
Additional testing‡ from the index consultation to day 30	335 (11%)	517 (14%)	0·83 (0·60–1·15)	2·0% (–1·7 to 5·0)	NA
Follow-up visits with their physician from the index consultation to day 30	770 (26%)	968 (26%)	0·86 (0·70–1·05)	2·8% (–0·9 to 6·1)	NA
Antibiotic prescribing after the consultation to day 30	291 (10%)	429 (11%)	0·77 (0·61–0·98)	2·4% (0·2 to 4·2)	NA
Exploratory endpoints					
Additional testing‡ at the index consultation	249 (8%)	400 (11%)	0·86 (0·86–0·86)	1·4% (1·4 to 1·4)	NA
Additional testing‡ day 1–30	111 (4%)	149 (4%)	0·87 (0·62–1·23)	0·5% (–0·9 to 1·5)	NA
Referral to hospital at the index consultation	24 (1%)	13 (<1%)	2·52 (1·03–6·19)	–0·5% (–1·8 to –0·0)	NA
Referral to hospital day 1–30	79 (3%)	84 (2%)	1·14 (0·76–1·71)	–0·3% (–1·5 to 0·5)	NA
Admission to hospital at the index consultation	7 (<1%)	11 (<1%)	0·80 (0·23–2·78)	0·1% (–0·5 to 0·2)	NA
Admission to hospital day 1–30	25 (1%)	53 (1%)	0·57 (0·35–0·92)	–0·6% (–0·9 to –0·1)	NA
Mortality at the index consultation	0	0	NA	NA	NA
Mortality day 1–30	0	0	NA	NA	NA
Full clinical recovery at day 7	2539 (85%)	3200 (85%)	1·01 (0·97–1·03)	0·1% (–0·4 to 0·4)	NA
Full clinical recovery at day 30	2967 (99%)	3747 (>99%)	1·00 (0·97–1·03)	0·0% (–0·0 to 0·0)	NA
Physician's adherence to the clinical decision tool					
Self-reported adherence	2826/2986 (95%)	NA	NA	NA	NA
Did not prescribe an antibiotic when the decision tree was scored negative and they were not considering antibiotics	2104/2126 (99%)	NA	NA	NA	NA
Did not prescribe an antibiotic when the decision tree was scored negative, they were considering antibiotics, and the POCT of CRP result was ≤5 mg/L	39/54 (72%)	NA	NA	NA	NA
Performed a CRP test when at least one of the questions in the decision tree was scored positive	429/495 (87%)	NA	NA	NA	NA
Performed a CRP test when the decision tree was scored negative and they were considering antibiotics	304/354 (86%)	NA	NA	NA	NA

Data are n (%), or mean (pooled SD), or n/N (%). aHR=adjusted hazard ratio. aMD=adjusted mean difference. aOR=adjusted odds ratio. aARR=adjusted absolute risk reduction. CRP=C-reactive protein. NA=not applicable. POCT=point-of-care testing. *aOR and aARR are used with binary outcomes, aHR and aMD are used with the time-to-event outcome. †Non-inferiority margins for coprimary endpoints tested for non-inferiority are 1 day for duration until clinical recovery, 3% for additional investigations from the index consultation to day 30, 4% for follow-up visits with their physician from the index consultation to day 30, and 2% for antibiotic prescribing after the index consultation to day 30. ‡Including, but not limited to, x-ray, blood tests, and urine tests.

Table 2: **Coprimary and exploratory outcomes**

antibiotics were prescribed contrary to decision-tree results or POCT of CRP was not performed when indicated.

A trial steering committee, data monitoring team, and ethics committee (from University Hospitals Leuven) supervised the trial. The data monitoring team consisted of members of KU Leuven (University of Leuven), representatives of KCE (Belgian Health Knowledge Centre), patient and public representatives, and medical and academic experts. All statistical analyses were performed with R.

Role of the funding source

The funder of the study provided feedback on the study design, but had no role in the conduct, data collection, data analysis, or data interpretation, the writing of the report, patient recruitment, or any other aspect pertinent to the study.

Results

Between Feb 24, 2021, and Dec 29, 2023, 178 potential practices (including 7049 potential participants) were screened, of which 171 practices were deemed eligible and randomly assigned to either the clinical decision tool (n=82) or usual care (n=89). 6760 eligible children from these 171 practices (2993 from the 82 practices assigned to the clinical decision tool, and 3767 from the 89 practices assigned to usual care) were subsequently included in the trial (figure 1). After recruitment, five children were excluded from each group. The final dataset included 2988 children from 82 intervention practices and 3762 children from 89 control practices, all of whom were treated according to the assigned study procedure. Data from the electronic patient diaries were obtained from 1322 (44%) children in the intervention group and 1427 (38%) children in the control group and were missing for 4001 (59%) participants in total. The trial concluded upon reaching the required sample size (including the 10% buffer), as per protocol.

Both groups were well matched at baseline (table 1; appendix pp 36–46). Most of the 6750 children included were boys (3447 [51%]), included by a general practitioner (6178 [92%]), and in the 2–6 years age category (3019 [45%]), with a median age of 3·8 years (IQR 1·8–7·0).

A smaller proportion of children managed with the clinical decision tool were prescribed antibiotics at the index consultation (immediate or delayed) compared with usual care (466 [16%] of 2988 *vs* 817 [22%] of 3762, aOR 0·72 [95% CI 0·55–0·94], aARR 5·1% [95% CI 1·0–8·5]; p=0·017; table 2). 60 (2%) children received two antibiotics at the index consultation, five of whom received a third antibiotic. Among the antibiotics prescribed during the index consultation, amoxicillin accounted for 1009 (75%) of the 1348 antibiotic prescriptions, with similar proportions of most antibiotic types between groups (appendix pp 47–48).

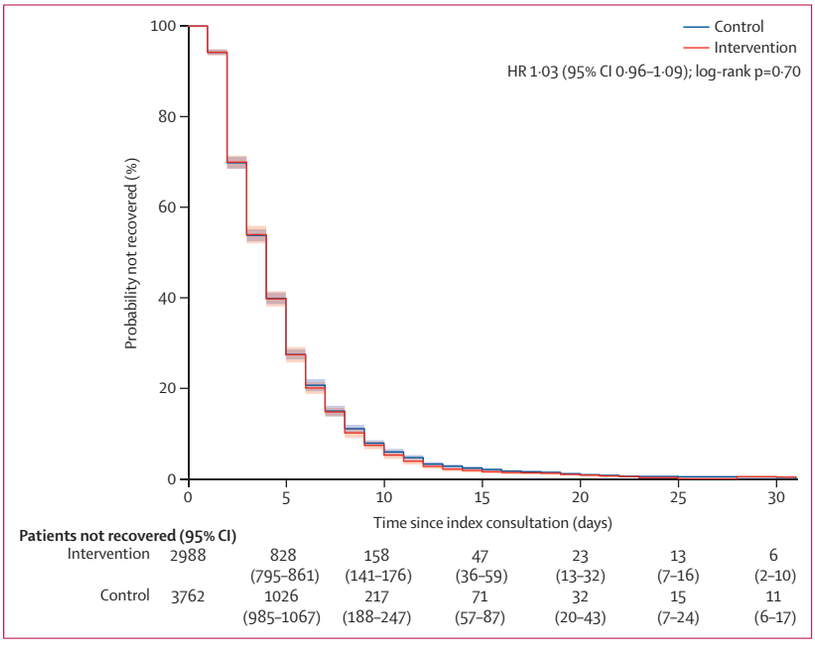

Figure 2: **Kaplan–Meier curves for the survival distributions over time for the control and the intervention group with full clinical recovery as the event of interest**

The red shaded area represents the 95% CI for the intervention group, and the blue shaded area represents the 95% CI for the control group. The numbers of patients not recovered between brackets under the figure also represent the 95% CIs. No data in this analysis were censored.

The upper limit of the 95% CIs did not exceed the prespecified non-inferiority margin for the other coprimary outcomes: mean days until full clinical recovery (4·6 [SD 3·5] with the clinical decision tool *vs* 4·7 [3·6] with usual care, aHR 1·03 [95% CI 0·96 to 1·09], aMD –0·1 days [–0·5 to 0·3]; figure 2), additional testing at either the index consultation or during follow-up (335 [11%] of 2988 *vs* 517 [14%] of 3762, aOR 0·83 [0·60 to 1·15], aARR 2·0% [–1·7 to 5·0]), follow-up visits (770 [26%] *vs* 968 [26%], aOR 0·86 [0·70 to 1·05], aARR 2·8% [–0·9 to 6·1]), and antibiotic prescribing after the index consultation (291 [10%] *vs* 429 [11%], aOR 0·77 [0·61 to 0·98], aARR 2·4% [0·2 to 4·2]; table 2). The proportional hazards assumption is supported (figure 2; appendix p 31).

In both the control and intervention groups, nearly half of the children (1753 [46·6%, 95% CI 45·4–47·8] of 3762 in the control group and 1375 [46·0%, 44·8–47·3] of 2988 in the intervention group) recovered by day 4, with 3360 (89·3%, 88·2–90·4) in the control group and 2679 (89·7%, 88·6–90·8) in the intervention group reaching recovery by day 9, and complete recovery observed by day 31. The accompanying log-rank test yielded a p value of 0·70, indicating no significant difference in recovery rates between the two groups (figure 2).

In the intervention group, 249 (8%) children received additional testing at the index consultation compared with 400 (11%) in the control group (aOR 0·86

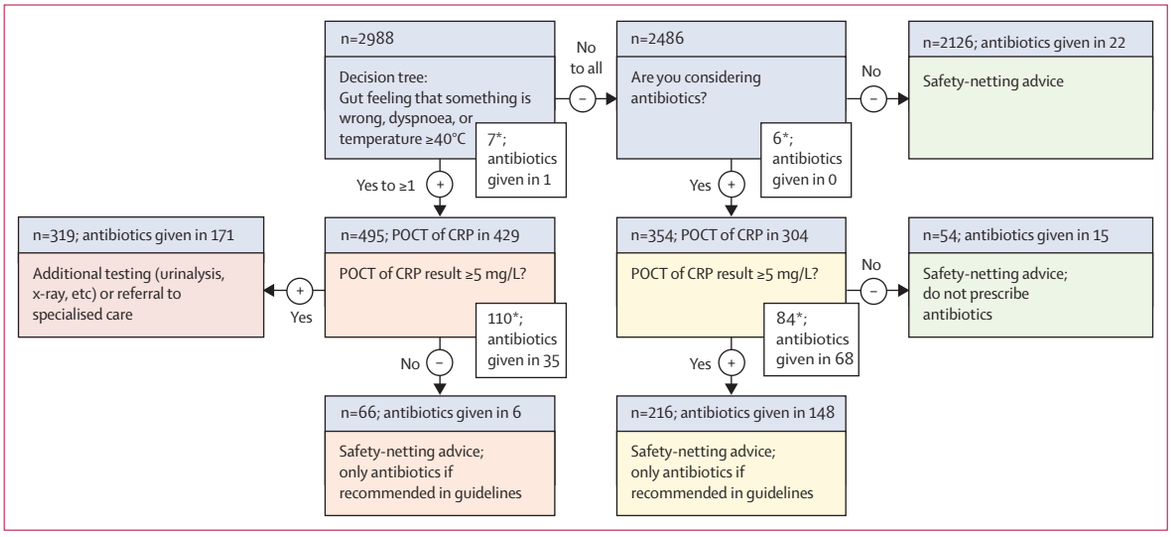

***Figure 3*: Clinical decision tool showing the number of children at each step, the number who received POCT of CRP, and the number receiving antibiotics at the final step**

POCT=point-of-care testing. CRP=C-reactive protein. *Number of children with missing or incomplete data.

[95% CI 0·86–0·86], aARR 1·4% [1·4–1·4]; table 2). The number of participants referred to hospital at the index consultation was 24 (1%) in the intervention group versus 13 (<1%) in the control group (aOR 2·52 [1·03–6·19], aARR –0·5% [–1·8 to –0·0]). There were 25 (1%) hospital admissions in the intervention group during follow-up and 53 (1%) in the control group (aOR 0·57 [0·35–0·92], aARR –0·6% [–0·9 to –0·1]). There were no between-group differences in hospital referrals or additional testing during follow-up, or in hospital admissions at index consultation (table 2); however, the study was not statistically powered to test these outcomes. No children died during the trial.

2539 (85%) children in the intervention group and 3200 (85%) in the control group reached full clinical recovery within 7 days (aOR 1·01 [0·97–1·03]; table 2). Within 30 days, nearly 100% in both groups reached full clinical recovery (2967 [99%] in the intervention group and 3747 [>99%] in the control group). For 2826 (95%) of 2986 patients in the intervention group, physicians reported adherence to the clinical decision tool (table 2). Of the 2126 children in the intervention group for whom the decision tree was negative and antibiotics were not considered, antibiotics were not prescribed in 2104 (99%; figure 3). When the decision tree was negative but antibiotics were considered and the POCT of CRP result was ≤5 mg/L, antibiotics were prescribed in 15 (28%) of 54 children; a full list of reasons are provided in the appendix (p 49), with the most common being bilateral otitis media, particularly in children younger than 2 years (seven [47%] of 15).

POCT of CRP was attempted in 733 (25%) children in the intervention group: 429 (87%) of 495 when the decision tree response had been yes and 304 (12%) of 2486 when the decision tree response had been no. Of these children, 120 (16%) had a CRP value of less than 5 mg/L (66 with a positive decision tree response and 54 with a negative decision tree response), 535 (73%) had a CRP value of at least 5 mg/L (319 with a positive decision tree response and 216 with a negative decision tree response), and CRP results were missing for 78 (11%). The median CRP value was 23 mg/L (IQR 11–46, range 5–181; appendix p 44).

During the 30-day follow-up period, 102 children were reported to have had an adverse event (36 [1%] of 2988 in the intervention group and 66 [2%] of 3762 in the control group; appendix pp 50–52), 90 of which were serious adverse events (all hospitalisation: 30 [1%] in the intervention group and 60 [2%] in the control group, aOR 0·63 [95% CI 0·40–0·97]). None of the physicians reported that the serious adverse events were caused by the study procedures. The most common final diagnosis made in the hospital was bronchiolitis or pneumonia (nine [25%] of 36 in the intervention group and 15 [23%] of 66 in the control group). One child (in the control group) hospitalised for petechiae and fever without focus was initially treated with empirical intravenous antibiotics but was later diagnosed with influenza.

Among the three age groups, the proportion of antibiotic prescribing both at and after the index consultation, as well as the proportion of children who had a follow-up visit, were highest in infants (ie, aged 6–12 months) and lowest in older children (ie, aged 7–12 years; appendix p 53). In contrast, the proportion of children receiving additional testing from the index consultation to day 30 was lowest in infants and highest in older children (appendix p 53). Summary estimates across age groups were consistent with the main analysis.

In the intervention group, antibiotic prescribing at the index consultation was slightly higher in boys than in

girls (appendix p 54). In both groups, additional testing from the index consultation to day 30 was more common in girls than in boys. Other results aligned with the main analysis (appendix p 54). Because of low sample sizes, we did not perform subgroup analyses for gender X (n=0) or for those who preferred not to say (n=1).

Results remained similar to the original analysis after removing data from 221 (3%) children from both groups from practices that did not meet the first criterion for consecutive inclusions and 524 (8%) children from practices that did not meet any of the three criteria (appendix pp 55–57).

In the per-protocol sensitivity analysis, omitting data from 152 (5%) of 2988 children in the intervention group reduced antibiotic prescribing at the index consultation to 370 (13%) of 2836 versus 817 (22%) of 3762 in the control group (aOR 0·56 [95% CI 0·42–0·74]; p<0·0001; appendix pp 58–59).

Discussion

This cluster-randomised controlled trial showed a safe reduction in antibiotic prescribing at the index consultation for children with acute illness presenting to ambulatory care when managed with the clinical decision tool, which included a validated decision tree to rule out serious infections requiring hospital admission, guided POCT of CRP based on the result of the decision tree and subsequent consideration as to whether antibiotics are indicated, and safety-netting advice, compared with usual care. This reduction did not negatively affect recovery time, additional testing, follow-up visits, or subsequent antibiotic prescribing. High physician adherence to this clinical decision tool supports its feasibility and acceptability in real-world practice.

The antibiotic prescribing proportion within the control group was 22%, closely matching the 23% observed in our 2022 Flemish general practitioner registry-based study.[8] Originally, the decision tree was developed to rule out a strict set of serious infections requiring hospital admission, and previous external validation showed high sensitivity at 100% (95% CI 71–100), whereas specificity was lower at 84% (82–85), resulting in a considerable number of false positives.[11] As the clinical decision tool did not increase hospital referrals or admissions, the addition of POCT of CRP in children at increased risk of a serious infection after a response of yes to any feature of the decision tree or when the physician still considered antibiotics when responding no to all features, as well as safety-netting advice, reduced unnecessary referrals to proportions at least similar to usual care.

Two UK-based, cluster-randomised, controlled trials of multifaceted interventions to reduce antibiotic prescribing for acute respiratory tract infections (RTIs) in primary care found no evidence of reduced prescribing for children (Blair and colleagues, 2023:[29] rate ratio 1·01 [95% CI 0·99–1·03]; Gulliford and colleagues, 2019:[30] rate ratio 0·96 [0·82–1·12]), possibly because they did not include POCT of CRP or a validated clinical prediction rule.

Our 2019 systematic review and meta-analysis[16] found that POCT of CRP significantly reduced immediate antibiotic prescribing in children only when guidance on antibiotic prescribing relative to CRP concentrations was provided (246 [32%] of 770 in the intervention [POCT of CRP] group *vs* 409 [44%] of 940 in the usual care group, risk ratio [RR] 0·56 [95% CI 0·33–0·95]) from two studies; I^2=79%; high-certainty evidence), without affecting patient satisfaction, clinical recovery, follow-up visits, further testing, or hospital admissions. We observed similar results in this study, with the exception that hospital admissions were not assessed for superiority and patient satisfaction will be evaluated later through a nested qualitative study. Similarly, the 2022 Cochrane systematic review update by Smedemark and colleagues[28] found that POCT of CRP likely reduces antibiotic prescribing for RTIs in children: 482 (37%) of 1314 in the intervention group versus 524 (51%) of 1021 in the standard care group, RR 0·78 (0·67–0·91) from four studies; I^2=45%; moderate-certainty evidence. The antibiotic prescribing proportions in these reviews are higher than those observed in our trial, but the estimated effect sizes were similar. We speculate that this discrepancy can be best attributed to the observed decline in antibiotic prescribing rates over the past 20 years; Smedemark and colleagues[28] included trials conducted in 2000, 2016, 2018, and 2019.[8] They recommend additional research in various subgroups and areas, particularly focusing on children, including established CRP cutoff values for withholding antibiotics and validating CRP decision algorithms. The ARON trial effectively addresses these issues.

In their 2024 randomised controlled trial, Jung and colleagues[31] found no reduction in antibiotic prescribing, compared with a control group not provided with POCT of CRP, for either children or adults with suspected lower RTI in primary care when arbitrarily guided POCT of CRP was used without a decision tree or safety-netting advice. Our 2025 systematic review and network meta-analysis[19] found that, compared with usual care, paper safety-netting advice for children with acute illness might reduce antibiotic prescribing (OR 0·66 [95% CI 0·53–0·82] from three studies with 35 988 participants; I^2=92%; very low certainty), antibiotic consumption (0·39 [0·27–0·58] from one study with 509 participants; low risk of bias), and return visits (0·74 [0·63–0·87] from two studies with 17 345 participants).

A multicentre, parallel-group, pragmatic, cluster-randomised, controlled trial design is the gold standard for evaluating the real-world effectiveness of interventions. Our study was conducted in many general practitioner and community paediatrician practices across Belgium. The trial team closely collaborated with academic centres, guaranteeing sufficient staff for training and support. The partnership with the Universitaire Ziekenhuizen Leuven

Clinical Trial Centre for data management and monitoring ensured high data integrity. The integration of our clinical decision tool into the eCRF mirrors its intended future implementation in electronic health records, providing a preview of the expected real-world adherence to the clinical decision tool. The high adherence rates underscore the feasibility and acceptability of the tool in everyday practice, which is crucial for successful implementation in wider clinical settings. The use of eCRFs and electronic patient diaries for follow-up ensures accurate and thorough data collection, enhancing the reliability of the results. Data from the electronic patient diaries were missing for 4001 (59%) of 6750 participants, consistent with similar studies. We mitigated this factor by using various imputation techniques, which confirmed the robustness of the results. Qualitative research suggests that to reduce unnecessary antibiotic prescriptions for children with RTIs, interventions should focus on increasing clinicians' confidence and prognostic certainty in safely withholding treatment and enhancing the ability of parents to assess illness severity.[32] The ARON trial likely boosted the confidence of clinicians to withhold antibiotics and the confidence of parents that antibiotics might not be required.

Our study also had some limitations. The trial design necessitated an unblinded approach, which could have influenced behaviour and reporting. Despite efforts to recruit practices pragmatically, there might still have been inherent selection bias due to voluntary participation, potentially skewing the sample towards more motivated practices. Selection bias could have also occurred in the recruitment of children because both the consenting parent and the recruiting physician could introduce systematic differences. A parent's decision to consent might be influenced by their degree of concern about their child, the severity of the child's illness, or other personal factors. Physicians, however, might select children who are less severely ill because these consultations allow more time to be spent on trial procedures. Conversely, intervention-group physicians might have enrolled more severely ill children, anticipating greater benefit from the intervention. These factors could lead to systematic differences in the recruited population. Using the consecutive-inclusions sensitivity analyses, we aimed to mitigate potential selection bias by identifying and addressing systematic differences in how physicians included children (not focusing on illness severity differences between study arms, specifically). Additionally, because physicians were being observed, they might have avoided prescribing antibiotics in some instances (known as the Hawthorne effect).[33] All physicians received training before their participation in the trial as described, which could have affected their prescribing behaviour. However, this education was limited to a review of existing, readily available guidelines and a few clinical case vignettes. Differences in health-care infrastructure, diagnostic protocols, and antibiotic prescribing practices outside Belgium might affect the generalisability of the results. Although our study included a diverse range of general practices across various settings, we acknowledge that the absence of race and ethnicity data could limit the assessment of potential variations in prescribing patterns among different racial or ethnic groups. The follow-up period of 30 days, although sufficient for assessing short-term outcomes (eg, complications, chronic infections, and the effect on gut microbiota), might not capture long-term adverse effects or the sustainability of reduced prescribing rates. However, longer follow-up times of up to 3 months will be used in the economic evaluation of the intervention, which will be reported in a subsequent publication.

Primary care has a pivotal role in combating antimicrobial resistance and our findings represent an important step forward in this effort. The clinical decision tool not only supported decision making in patients with suspected serious infection, but also provided guidance when serious infection was unlikely, ensuring alignment with national guidelines and safety-netting advice to promote appropriate antibiotic use. By integrating POCT of CRP within a structured framework, the tool helped both to rule out serious infections in children at high risk and to guide antibiotic prescribing in children in whom serious infection had likely been ruled out. This study highlights the effectiveness of a comprehensive approach to managing infection in children with acute illness in ambulatory care, combining a validated decision tree, guided POCT of CRP, and safety-netting advice. By presenting a safe and evidence-based strategy for reducing unnecessary antibiotic prescribing, our findings contribute to the global fight against antimicrobial resistance.

Our findings also support the dissemination and implementation of the clinical decision tool according to evidence-based strategies tailored to each specific context.[34] Testing and adapting it specifically for rural and remote areas, as well as low-income and middle-income countries where the effect of antimicrobial resistance is most substantial,[1,35] is an important step towards broader implementation. Clinical guidelines could be adapted to incorporate the clinical decision tool and electronic health records could integrate it as part of a clinical-decision support system. Key steps for broader adoption include reimbursing POCT of CRP and establishing a legal framework for POCT outside the hospital.[36] The safety-netting advice booklet might be even more effective if it were expanded to a multimodal format, including a website and mobile app, as recommended by parents and clinical experts.[18]

This study has shown the clinical effectiveness of the pragmatic implementation of the ARON trial's clinical decision tool; however, to justify broader implementation, further investigation is needed into the long-term effects on antimicrobial resistance, budget implications, cost-effectiveness for health-care payers, and potential equity considerations (ie, clinical and patient-reported outcomes).

Once the dissemination and implementation strategies are widely adopted, re-evaluation is important to measure changes over time in physician uptake of and adherence to the clinical decision tool. For this, we could use audit tools or continuous quality-improvement programmes, which can measure clinical outcomes and identify actual change in practice.[37] We should aim to identify factors that contribute to sustained improvements in antibiotic prescribing and assess the effectiveness of different implementation strategies.

The ARON trial shows that a clinical decision tool combining a validated decision tree, guided POCT of CRP, and safety-netting advice can avoid one in four antibiotic prescriptions for acutely ill children in primary care without causing harm. Given the potential of a clinical decision tool to considerably improve the clinical management of children with acute illness and its positive effect on patients and public health, these findings on clinical effectiveness support the broader dissemination and implementation within ambulatory care.

Contributors

JYV, AVdB, SC, SA, JL, and ADS developed the original idea. JYV led the funding applications with input from AVdB, JL, ADS, SA, and SC. The protocol was developed by JYV, TDB, AVdB, ADS, AL, and JL. Study progress was supervised by JYV, TDB, RB, ED, LDR, and MD. JYV, TDB, RB, ED, LDR, and AL developed the statistical analysis plan and interpreted the analyses, with input from all the authors. JYV, RB, and ED did the statistical analysis supervised by AL. JYV, RB, ED, and TDB led the writing of the paper and all authors contributed to interpretation of the analyses and to revisions of the paper. JYV, TDB, RB, ED, and AL accessed and verified the data. All authors had full access to all the data for this study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual patient data from this trial will not be published in the public domain. Deidentified participant data is available for further analyses upon request. Requests for data, with justification, should be sent to JYV (jan.verbakel@kuleuven.be), TDB (ruben.burvenich@kuleuven.be), or RB (tine.deburghgraeve@kuleuven.be). The trial protocol is available online for an indefinite period (https://gbiomed.kuleuven.be/english/research/50000687/luhtar/research/poct).

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