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# Impact of a clinical decision rule on antibiotic prescription for children with suspected lower respiratory tract infections presenting to European emergency departments: a simulation study based on routine data

**Nienke N. Hagedoorn[1], Josephine H. L. Wagenaar[1], Daan Nieboer[2], David Bath[3], Ulrich Von Both[4,5], Enitan D. Carrol[6,7,8], Irini Eleftheriou[9], Marieke Emonts[10,11,12], Michiel Van Der Flier[13,14,15], Ronald De Groot[13,14], Jethro Herberg[16], Benno Kohlmaier[17], Michael Levin[16], Emma Lim[10,11,12], Ian Maconochie[18], Federico Martinon-Torres[19], Ruud Nijman[16], Marko Pokorn[20], Irene Rivero Calle[19], Maria Tsolia[9], Shunmay Yeung[3,21], Dace Zavadska[22], Werner Zenz[17], Clementien L. Vermont[23], Rianne Oostenbrink[1] and Henriëtte A. Moll [1]* on behalf of the PERFORM consortium†**

*[1]Department of General Paediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; [2]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [3]Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, London, UK; [4]Division of Paediatric Infectious Diseases, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-University, Munich, Germany; [5]Partner site Munich, German Center for Infection Research (DZIF), Germany; [6]Institute of Infection, Veterinary and Ecological Sciences Global Health Liverpool, University of Liverpool, UK; [7]Alder Hey Children's NHS Foundation Trust, Liverpool, UK; [8]Liverpool Health Partners, Liverpool, UK; [9]Second Department of Paediatrics, National and Kapodistrian University of Athens, P. & A. Kyriakou Children's Hospital, Athens, Greece; [10]Paediatric Immunology, Infectious Diseases & Allergy, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [11]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK; [12]NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, UK; [13]Paediatric Infectious Diseases and Immunology, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, The Netherlands; [14]Section Paediatric Infectious Diseases, Laboratory of Medical Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands; [15]Paediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [16]Section of Paediatric Infectious Diseases, Imperial College London, London, UK; [17]Department of General Paediatrics, Medical University of Graz, Graz, Austria; [18]Paediatric Emergency Medicine, Imperial College Healthcare NHS Trust, London, UK; [19]Genetics, Vaccines, Infections and Paediatrics Research Group (GENVIP), Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [20]Department of Infectious Diseases, University Medical Centre Ljubljana, University of Ljubljana, Ljubljana, Slovenia; [21]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK; [22]Department of Paediatrics, Children's Clinical University Hospital, Rīgas Stradiņa universitāte, Riga, Latvia; [23]Department of Paediatric Infectious diseases and Immunology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*

*Corresponding author. E-mail: h.a.moll@erasmusmc.nl
†Members of the PERFORM consortium are listed in the Supplementary data, available at *JAC* Online.

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**Background:** Discriminating viral from bacterial lower respiratory tract infections (LRTIs) in children is challenging thus commonly resulting in antibiotic overuse. The Feverkidstool, a validated clinical decision rule including clinical symptoms and C-reactive protein, safely reduced antibiotic use in children at low/intermediate risk for bacterial LRTIs in a multicentre trial at emergency departments (EDs) in the Netherlands.

**Objectives:** Using routine data from an observational study, we simulated the impact of the Feverkidstool on antibiotic prescriptions compared with observed antibiotic prescriptions in children with suspected LRTIs at 12 EDs in eight European countries.

**Methods:** We selected febrile children aged 1 month to 5 years with respiratory symptoms and excluded upper respiratory tract infections. Using the Feverkidstool, we calculated individual risks for bacterial LRTI retrospectively. We simulated antibiotic prescription rates under different scenarios: (1) applying effect estimates on antibiotic

prescription from the trial; and (2) varying both usage (50%–100%) and compliance (70%–100%) with the Feverkidstool's advice to withhold antibiotics in children at low/intermediate risk for bacterial LRTI (≤10%).

**Results:** Of 4938 children, 4209 (85.2%) were at low/intermediate risk for bacterial LRTI. Applying effect estimates from the trial, the Feverkidstool reduced antibiotic prescription from 33.5% to 24.1% [pooled risk difference: 9.4% (95% CI: 5.7%–13.1%)]. Simulating 50%–100% usage with 90% compliance resulted in risk differences ranging from 8.3% to 15.8%. Our simulations suggest that antibiotic prescriptions would be reduced in EDs with high baseline antibiotic prescription rates or predominantly (>85%) low/intermediate-risk children.

**Conclusions:** Implementation of the Feverkidstool could reduce antibiotic prescriptions in children with suspected LRTIs in European EDs.

## Introduction

Discriminating viral from bacterial aetiology in lower respiratory tract infections (LRTIs) is challenging, due to similarities in clinical symptoms and the absence of a gold standard.[1] Despite the implementation of national guidelines,[2] antibiotic prescription rates for LRTIs are high and vary widely (27%–84%) at European emergency departments (EDs), suggesting overtreatment.[2,3] Unnecessary antibiotic prescriptions can lead to adverse effects, additional costs and antimicrobial resistance.[4–6] Therefore, unnecessary antibiotic prescriptions should be reduced in children at low risk for bacterial LRTIs.

Clinical decision rules can be useful in reducing antibiotic prescribing.[7,8] Nijman *et al.*[9] developed the Feverkidstool, which predicts serious bacterial infections and specifies the individual probability of children having bacterial pneumonia, based on clinical parameters and C-reactive protein (CRP) level. To reduce antibiotic treatment, the Feverkidstool advises to withhold antibiotic prescription for patients at low/intermediate risk for having bacterial LRTI. The Feverkidstool has been extensively validated[8–11] and its effect on antibiotic prescriptions was evaluated in a stepped-wedge cluster-randomized multicentre study in EDs in the Netherlands.[12] In this intervention trial, antibiotic prescription in usual care was compared with antibiotic prescription using the advice of the Feverkidstool: withholding antibiotics for patients at low/intermediate risk for bacterial pneumonia (≤10%) or antibiotic prescription at the discretion of the physician for patients at high risk (>10%). This did not result in overall reduction of antibiotic prescribing in all patients, but it did achieve a reduction of antibiotic prescription in low/intermediate-risk patients as well as less therapy failure amongst high-risk patients. Moreover, in low/intermediate-risk patients the withholding of antibiotics did not influence therapy failure and thus was shown to be safe. The proportion of low/intermediate-risk patients was lower in the intervention trial than was estimated in the power calculations. The authors discussed that the potential effect of the Feverkidstool is related to the proportion of low/intermediate-risk patients and that its effect might be larger in settings with more low/intermediate-risk patients or higher baseline prescription rates.

Besides the differences in patient population, the potential impact of the Feverkidstool on antibiotic prescription is influenced by differences in uptake, including usage and compliance rates. In both clinical trials and observational studies at EDs, clinical decision rules were calculated in 50%–93% (usage rate),[12–17] whilst the treatment advice was followed in 80%–96% (compliance rate).[2,10,12–14,16,18] In addition, it is not evident that the effects from the intervention trial can be extrapolated to other European countries due to differences in the proportion of low/intermediate-risk patients and baseline prescription rates in LRTIs at European EDs.[8]

A clinical study to assess the prospective impact of the Feverkidstool in European EDs would be expensive and time-consuming and would expose children to additional investigations, whereas a simulation study is an efficient method to evaluate its effect under different scenarios for the uptake of the decision rule and, on top of that, its effect in different patient populations.[19,20] Using routine data, this study aims to simulate the potential impact of the Feverkidstool on antibiotic prescription rates in children with suspected LRTIs at European EDs compared with observed antibiotic prescriptions.

## Patients and methods

### *Study design and population*

This study is a secondary analysis of data collected as part of the Management and Outcome of Fever in Children in Europe (MOFICHE) study, which is embedded in the Personalized Risk assessment in Febrile illness to Optimize Real-life Management across the European Union (PERFORM) project (www.perform2020.org). MOFICHE is an observational study performed in 12 EDs in university or large teaching hospitals in eight different European countries: Austria, Germany, Greece, Latvia, the Netherlands ($n = 3$), Spain, Slovenia and the UK ($n = 3$). Study design and details regarding these EDs have previously been described.[21,22] The STROBE reporting guideline was followed.

In short, MOFICHE included routine data of children aged <18 years with a temperature of ≥38.0°C measured at the ED or a history of fever in the 72 h before the ED visit. For this study, we focused the main analysis on children >1 month to 5 years of age with suspected LRTI. Following inclusion and exclusion criteria of the intervention trial, we selected children with respiratory symptoms, defined as coughing and/or increased work of breathing. We excluded children with a single clinical focus of upper respiratory tract infection, children with therapeutic antibiotic treatment up to 7 days prior to the ED visit and children with relevant comorbidity, i.e. a condition in ≥2 organ systems, or immunodeficiency, malignancy, cardiac condition, psychomotor delay or prematurity (born before gestational age of 32 weeks and <1 year of age at the time of presentation).[9,12] For subanalysis, we also included children aged 5–12 years and 12–18 years with suspected LRTIs according to aforementioned inclusion and exclusion criteria.

Collected data included age, sex, comorbidity,[23] type of referral (self-referral, GP, private paediatrician, emergency medical services or other) and triage urgency. In addition, we collected the presence of ill appearance, vital signs (heart rate, respiratory rate, oxygen saturation, temperature, capillary refill time) and diagnostic data including laboratory results (CRP level), imaging and microbiological results. We collected the presumed

focus of infection by the physician after assessment at the ED, and hospital admission or ICU admission following the ED visit. We recorded antibiotic prescription (type, route of administration) at the ED or in the first 24 h of hospital admission.[21]

### Outcome

The primary outcome was the difference between observed antibiotic prescription rates and antibiotic prescription rate after simulating the implementation of the Feverkidstool in different scenarios.

### Missing data

Vital signs marked as normal were given a normal value based on age-adjusted Advanced Paediatric Life Support (APLS) ranges.[24] CRP values marked as normal were given a value in the range 0–8 mg/L.[25] Missing values of the predictor variables of the Feverkidstool, including missing CRP level, were multiple imputed (MICE package). The imputation model included covariates of the Feverkidstool and auxiliary variables associated with urgency, disease severity, diagnostics, working diagnosis and antibiotic treatment. Patients with missing values for antibiotic prescription were excluded from analysis.

### Simulation

We retrospectively calculated individual risk scores of having a bacterial LRTI based on the original Feverkidstool algorithm. The Feverkidstool included the following variables: age <1 year; age ≥1 year; sex; fever duration; temperature; tachypnoea and tachycardia defined by APLS;[24] oxygen saturation <94%; capillary refill time ≥3 s; increased work of breathing; ill appearance; and CRP level (details in Table S1, available as Supplementary data at *JAC* Online).[9] A risk threshold of 10%, based on earlier research,[8,9,12] was used to classify patients at low/intermediate risk (≤10%) or high risk (>10%) for bacterial LRTI. Characteristics of the low/intermediate-risk versus high-risk groups were compared using chi-squared tests, independent *t*-tests and Mann–Whitney *U*-tests. Results with a *P* value <0.05 were deemed significant.

The effect of the Feverkidstool on antibiotic prescriptions was simulated using five strategies: (1) applying the effect estimates on antibiotic prescription from the intervention trial; (2) sensitivity analysis showing the effect of different combinations of usage and rates of compliance with the Feverkidstool's advice; (3) subgroups of each separate ED; (4) the transferability of the Feverkidstool's effect to older age groups (5–12 years, 12–18 years) and; (5) sensitivity analysis on complete cases for CRP data. The differences between observed prescription rates with simulated prescription rates were quantified by risk differences (RDs) and risk ratios (RRs).[26] All simulations were calculated separately for each of the 12 EDs and were pooled using a random-effects model (metafor package).

For the first simulated strategy, we simulated antibiotic prescription rates under the assumption that implementation of the Feverkidstool would have equal effect on antibiotic prescription as in the intervention trial.[12] In the trial, the pre-intervention prescription rate was 17% in the low/intermediate-risk group and 47% in the high-risk group. The adjusted ORs for antibiotic prescription after implementing the Feverkidstool were 0.31 (95% CI: 0.12–0.81) for the low/intermediate-risk group and 2.28 (95% CI: 0.84–6.17) for the high-risk group. To estimate the overall prescription rate after simulating the implementation of the Feverkidstool, we sampled ORs ($n = 1000$) based on the results from the intervention trial (estimated effect and standard error) and applied these to the routine data to obtain the simulated prescription rate and associated uncertainty after implementing the Feverkidstool. Separate ORs were sampled for the low/intermediate-risk and high-risk groups.

For the sensitivity analysis, we simulated the effect of the Feverkidstool on antibiotic prescription for varying usage rates (50%–100%) combined with varying compliance rates (70%–100%). These rates were chosen according to published impact studies of clinical decision rules in the ED: usage rates (50%–93%)[12–17] and compliance rates (80%–96%) where the average compliance rate was ∼90%.[2,10,12–14,16,18] Usage and compliance rates were modelled using a uniform random distribution at patient level, meaning that every patient had the same probability of usage or compliance. The usage rate was modelled as the percentage of patients for whom the Feverkidstool risk score was calculated. For these children, the compliance rate was modelled as the percentage of patients for whom physicians followed the advice of the Feverkidstool. Compliance resulted in withholding of antibiotics for low/intermediate-risk patients, whilst non-compliance resulted in antibiotic prescriptions to low/intermediate-risk patients despite advice to withhold them. In high-risk patients, we assumed that antibiotic treatment was as observed in the data. For this analysis of varying compliance rates, we assumed that the simulated antibiotic rates could not exceed observed prescription rates.

Third, we simulated the effect estimates of the intervention trial in each ED separately to provide insight on the Feverkidstool's effect in populations with different antibiotic prescription rates and different distribution of low/intermediate-risk patients. Fourth, we evaluated the transferability of the Feverkidstool's effect to older age groups with suspected LRTIs including 5–12 years and 12–18 years. Last, since we imputed CRP level for the main analyses, a sensitivity analysis was performed on complete cases: all analyses were repeated in children with CRP data available. Statistical analyses were performed in R version 3.6.

### Ethics

The study was approved by all the participating hospitals. No informed consent was needed for this study. Ethics Committee details for each country are as follows: Austria (Ethikkommission Medizinische Universitat Graz, ID: 28–518 ex 15/16); Germany (Ethikkommission Bei Der LMU München, ID: 699-16); Greece (Ethics committee, ID: 9683/18.07.2016); Latvia (Centrala medicinas etikas komiteja, ID: 14.07.2016. No. Il 16-07-14); Slovenia (Republic of Slovenia National Medical Ethics Committee, ID: 0120-483/2016-3); Spain (Comité Autonómico de Ética de la Investigación de Galicia, ID: 2016/331); The Netherlands (Commissie Mensgebonden onderzoek, ID: NL58103.091.16); and the UK (Ethics Committee, ID: 16/LO/1684, IRAS application no. 209035, Confidentiality advisory group reference: 16/CAG/0136). In the UK, an 'opt-out' procedure was used for this study.

## Results

### Study population

Of 38 480 febrile children, 13 984 patients aged 1 month to 5 years with respiratory symptoms were eligible for the main analysis. We excluded 7896 (56.5%) patients with solely upper respiratory infections, 429 (3.1%) with relevant comorbidity, 675 (4.8%) patients due to antibiotic treatment in the week prior to the ED visit and 46 (0.3%) with missing information on antibiotic prescription. This resulted in 4938 included patients [female: $n = 2122$, 42.9%; median age 1.8 years (IQR: 0.9–2.9)] (Table S2). Supplemental oxygen was provided to 459 (9.3%) patients. Following their ED visit, 2038 patients (41.3%) were admitted to a general ward and 29 (0.6%) to an ICU. CRP level was measured for 2409 patients [48.8%, median CRP level: 19 mg/L (IQR: 5–52)]. Characteristics of patients with and without CRP measurement are provided in Table S3.

Simulation of the Feverkidstool resulted in a median risk score of 2.9% (IQR: 1.5%–6.3%) for bacterial LRTI. Characteristics of the low/intermediate-risk group ($n = 4209$, 85.2%) and the high-risk group ($n = 729$, 14.8%) for bacterial LRTI are presented in Table 1.

**Table 1.** Descriptive characteristics of the study population stratified by risk groups based on the Feverkidstool risk score for bacterial LRTI

| | Low/intermediate-risk group (≤10%) *N* = 4209 | Missing values *n* (%) | High-risk group (>10%) *N* = 729 | Missing values *n* (%) |
|---|---|---|---|---|
| Female, *n* (%) | 1785 (42.4) | | 337 (46.2) | |
| Age, years, median (IQR) | 1.7 (0.9–2.9) | | 1.9 (1.3–2.8) | |
| Simple comorbidity, *n* (%) | 487 (11.6) | 61 (1.5) | 124 (17.0) | 9 (1.2) |
| Way of referral, *n* (%) | | 82 (1.9) | | 13 (1.8) |
| Self-referral | 2270 (53.9) | | 240 (32.9) | |
| GP or private paediatrician | 897 (21.3) | | 307 (42.1) | |
| Emergency medical service | 579 (13.8) | | 105 (14.4) | |
| Other healthcare professionals | 381 (9.1) | | 64 (8.8) | |
| High triage urgency[a], *n* (%) | 1584 (37.6) | 122 (2.9) | 387 (53.1) | 46 (6.3) |
| Clinical symptoms | | | | |
| Ill appearance, *n* (%) | 680 (16.2) | 218 (5.2) | 292 (40.1) | 53 (7.3) |
| Coughing, *n* (%) | 4012 (95.3) | 100 (2.4) | 673 (92.3) | 31 (4.3) |
| Fever duration, days, median (IQR) | 1.5 (0.5–3) | 341 (8.1) | 3 (1.5–5) | 54 (7.4) |
| Temperature, °C, median (IQR) | 37.6 (36.9–38.3) | 250 (5.9) | 38.3 (37.5–39.0) | 53 (7.3) |
| Increased work of breathing, *n* (%) | 1214 (28.8) | 327 (7.8) | 459 (63.0) | 67 (9.2) |
| Tachypnoea, *n* (%) | 1342 (31.9) | 785 (18.7) | 416 (57.1) | 176 (24.1) |
| Tachycardia, *n* (%) | 1455 (34.6) | 288 (6.8) | 453 (62.1) | 39 (5.4) |
| Capillary refill time ≥3 s, *n* (%) | 69 (1.6) | 480 (11.4) | 18 (2.5) | 134 (18.4) |
| Hypoxia, *n* (%) | 86 (2.0) | 485 (11.5) | 328 (45.0) | 55 (7.5) |
| Management | | | | |
| Chest X-ray performed, *n* (%) | 1293 (30.7) | 1 (0.0) | 425 (58.3) | 2 (0.3) |
| CRP, mg/L, median (IQR) | 13 (4–35) | 2939 (54.0) | 64 (29–129) | 296 (32.6) |
| Oxygen therapy, *n* (%) | 252 (5.9) | 14 (0.33) | 207 (28.4) | 8 (1.1) |
| Airway/breathing lifesaving interventions[b], *n* (%) | 68 (1.6) | | 45 (6.2) | |
| Haemodynamic interventions[c], *n* (%) | 27 (0.6) | | 10 (1.4) | |
| Admission to ward, *n* (%) | 1519 (36.1) | 5 (0.1) | 519 (71.2) | 1 (0.1) |
| Admission to ICU, *n* (%) | 16 (0.4) | | 13 (1.8) | |

[a]High triage urgency included patients with urgency levels of 'immediate', 'very urgent' and 'urgent'.
[b]Airway/breathing lifesaving interventions are defined as the need for a non-rebreathing mask, non-invasive ventilation, intubation or ventilation.
[c]Haemodynamic lifesaving interventions are defined as the need for IV or intra-ossal fluid resuscitation, intra-ossal access or blood administration.

Compared with high-risk patients, low/intermediate-risk patients were more often self-referred and more frequently triaged as low urgency ($P < 0.01$). High-risk patients had a higher need for oxygen therapy and higher admission rates to the ward or the ICU ($P < 0.01$) than low/intermediate-risk patients.

### *Simulation of effect estimates from the intervention trial on antibiotic prescription*

The overall observed antibiotic prescription rate was 33.5% (1656/4938), similar to the weighted prescription rate per ED (33.5%). In low/intermediate-risk patients, the observed antibiotic prescription rate was 29.6% (1247/4209) and in high-risk patients it was 56.1% (409/729). Applying the effects estimates from the intervention trial [adjusted ORs for antibiotic prescription: low/intermediate-risk group: 0.31 (95% CI: 0.12–0.81); high-risk group: 2.28 (95% CI: 0.84–6.17)] reduced overall antibiotic prescriptions from 33.5% to 24.1% [pooled RD: 9.4% (95% CI: 5.7%–13.1%); pooled RR 0.72 (95% CI: 0.63–0.81)].

### *Varying usage and compliance rates*

Simulating the Feverkidstool with 100% usage and compliance reduced overall antibiotic prescriptions from 33.5% to 9.9% [pooled RD: 23.6% (95% CI: 19.2%–28.0%); pooled RR 0.28 (95% CI: 0.22–0.36)]. Both usage rates and compliance rates influenced the effect on antibiotic prescription rate. Simulating usage rates from 50%–90%, combined with 100% compliance with the Feverkidstool, resulted in a reduction of antibiotic prescription [50% usage: pooled RD 11.8% (95% CI: 9.6%–14.0%); 90% usage: pooled RD 21.1% (95% CI: 17.0%–25.1%)] (Figure 1, Table S4). Assuming 100% usage, a minimum compliance rate of 78% was needed to achieve a significant reduction [pooled RD 4.9% (95% CI: 0.2%–9.7%)]. Combining usage rates of 50%–100% with 90% compliance resulted in overall antibiotic reductions ranging from 8.3% to 15.8%.

### *Subgroup analysis of each ED*

Between EDs, observed overall antibiotic prescription rates varied between 20.0% and 44.4%. Simulation of the effect estimates of

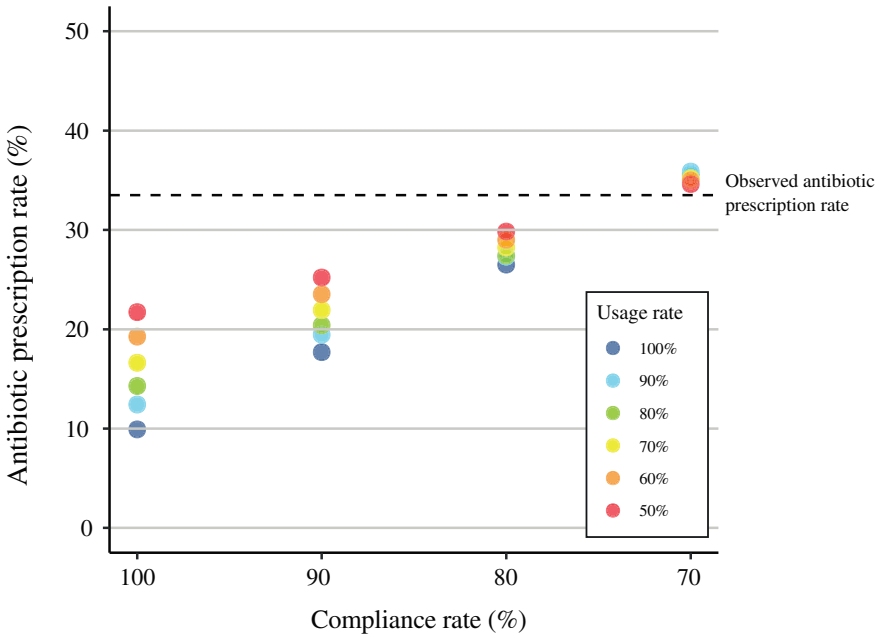
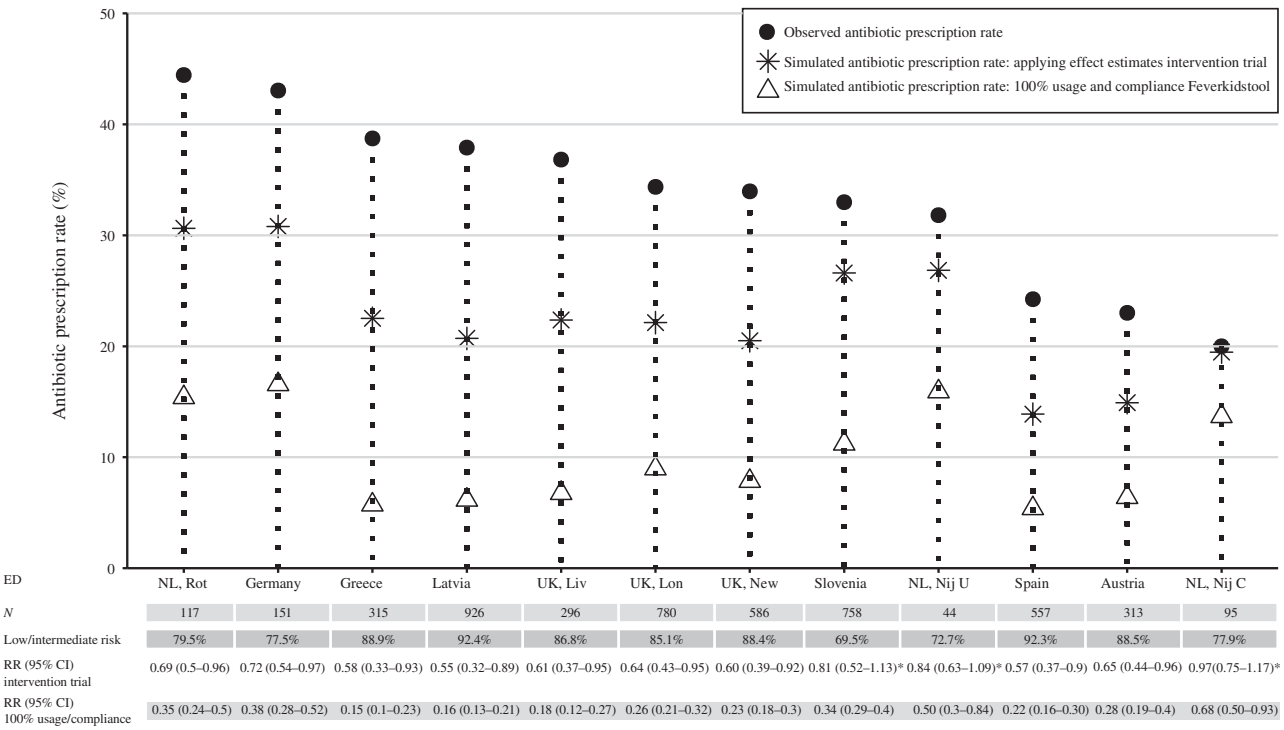



**Figure 1.** Antibiotic prescription rate simulated by implementing the Feverkidstool with varying usage and compliance rates. Presented data are based on pooled data from 12 EDs. Detailed information on simulation of the varying usage and compliance rates is presented in Table S4. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC* .




| ED | NL, Rot | Germany | Greece | Latvia | UK, Liv | UK, Lon | UK, New | Slovenia | NL, Nij U | Spain | Austria | NL, Nij C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *N* | 117 | 151 | 315 | 926 | 296 | 780 | 586 | 758 | 44 | 557 | 313 | 95 |
| Low/intermediate risk | 79.5% | 77.5% | 88.9% | 92.4% | 86.8% | 85.1% | 88.4% | 69.5% | 72.7% | 92.3% | 88.5% | 77.9% |
| RR (95% CI) intervention trial | 0.69 (0.5–0.96) | 0.72 (0.54–0.97) | 0.58 (0.33–0.93) | 0.55 (0.32–0.89) | 0.61 (0.37–0.95) | 0.64 (0.43–0.95) | 0.60 (0.39–0.92) | 0.81 (0.52–1.13)* | 0.84 (0.63–1.09)* | 0.57 (0.37–0.9) | 0.65 (0.44–0.96) | 0.97(0.75–1.17)* |
| RR (95% CI) 100% usage/compliance | 0.35 (0.24–0.5) | 0.38 (0.28–0.52) | 0.15 (0.1–0.23) | 0.16 (0.13–0.21) | 0.18 (0.12–0.27) | 0.26 (0.21–0.32) | 0.23 (0.18–0.3) | 0.34 (0.29–0.4) | 0.50 (0.3–0.84) | 0.22 (0.16–0.30) | 0.28 (0.19–0.4) | 0.68 (0.50–0.93) |

**Figure 2.** Antibiotic prescription rates simulated by applying effect estimates from the intervention trial and for 100% usage and compliance for each ED. Liv, Liverpool; Lon, London; New, Newcastle; Nij C, Nijmegen, Canisius; Nij U; Nijmegen, RadboudUMC; NL, Netherlands; Rot, Rotterdam. EDs are sorted according to observed antibiotic prescription rates. Details of the analysis are presented in Table S5. *RR not significant.

the intervention trial resulted in a reduction in all 12 EDs and was significant in 9 EDs [range of RD: 8.1% (95% CI: 0.8%–12.8%) to 17.2% (95% CI: 4.1%–25.8%)] (Figure 2). EDs with significant reductions had either large proportions of low/intermediate-risk patients (>85% in seven EDs) or high observed antibiotic prescription rates (>35% in five EDs) (Table S5).

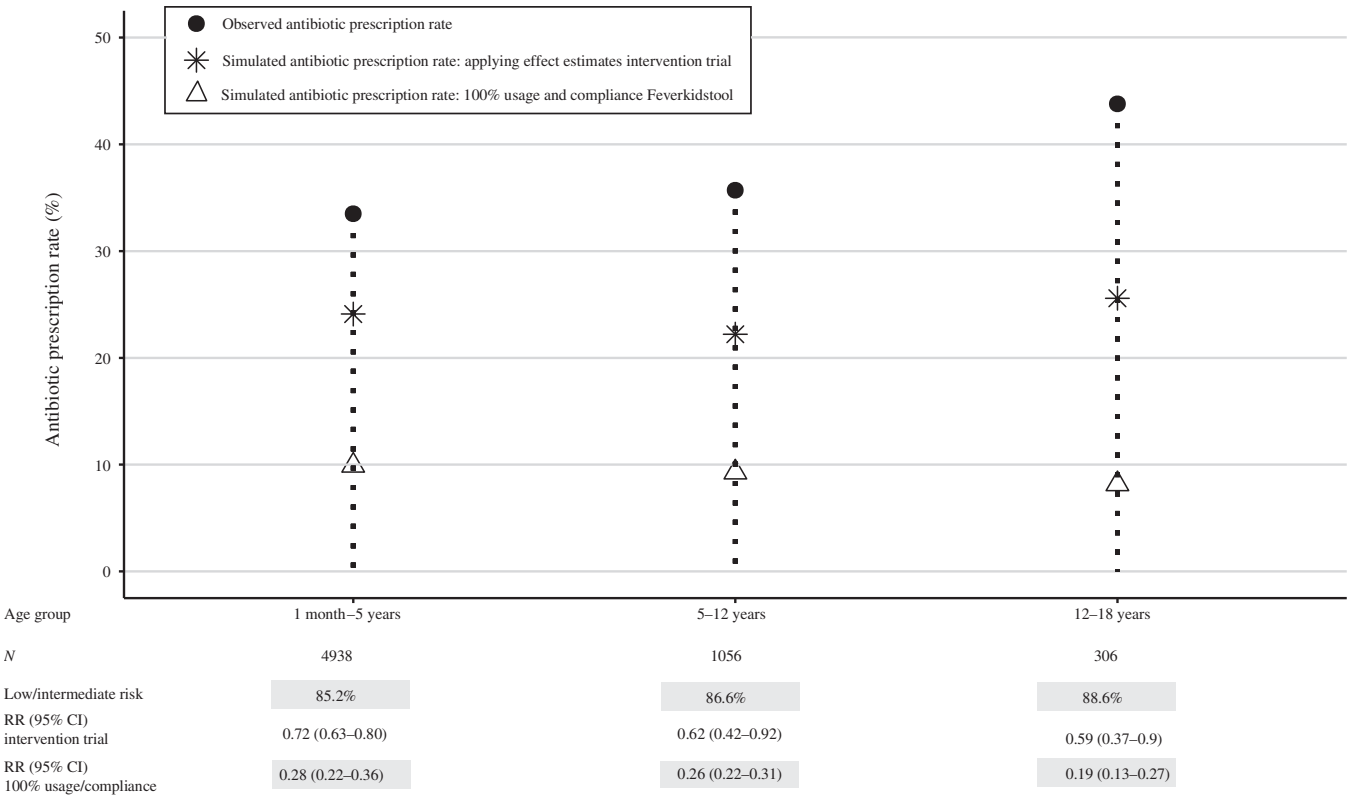



**Figure 3.** Antibiotic prescription rates simulated by applying effect estimates from the intervention trial and for 100% usage and compliance with the Feverkidstool for the age group 1 month to 5 years and its transferability to children aged 5–12 years and 12–18 years. Details of this analysis are presented in Table S6.

### *Transferability to older children*

In the age range 1 month to 18 years, 6300 children were eligible with suspected LRTIs. Of those, the majority were aged 1 month to 5 years (78.4%; 4938/6300). Children aged 5–12 years accounted for 16.7% (1056/6300) and children aged above 12 years for 4.9% (306/6300) of this population. In children aged 5–12 years and 12–18 years, the observed antibiotic prescription rates were 35.7% (377/1056) and 43.8% (134/306), respectively. In both these age groups, antibiotic prescriptions were reduced by applying effect estimates from the intervention trial [5–12 years: RD 13.4% (95% CI: 2.0%–20.8%); 12–18 years: RD 17.9% (95% CI: 4.0%–27.6%)] (Figure 3, Table S6 and Figure S1).

### *Complete cases for CRP*

The sensitivity analysis involving the population of only children that had CRP performed ($n = 2409$), showed similar results to those found in all analyses [pooled RD intervention trial: 13.5% (95% CI: 10.0%–17.1%); pooled RD 100% usage/compliance: 34.6% (95% CI: 26.8%–42.4%)] (Table S7).

## Discussion

Based on the data of routine care of febrile children in EDs in Europe, we simulated the potential effect of implementing the Feverkidstool on antibiotic prescription rates in children with suspected LRTIs compared with observed prescriptions. Simulating the effect estimates of the intervention trial reduced antibiotic prescriptions in routine care from 33.5% to 24.1%,[12] whereas 100% usage of and compliance with the Feverkidstool resulted in a reduction of antibiotic prescriptions to 9.9%. With usage rates varying from 50% to 100% and a compliance rate of 90%, antibiotic prescription reductions ranged from 8.3% to 15.8%. Subgroup analysis showed that the largest reduction of antibiotic prescription was observed in EDs with high antibiotic prescription rates or high prevalence of low/intermediate-risk patients.

Our study has some limitations. First, our study is based on simulating assumptions and, accordingly, results are estimates of the potential impact on antibiotics prescribing. Ideally, to reach maximum level of evidence, a multicentre intervention trial should be performed to assess the broad impact of a clinical decision rule.[27,28] However, it is expensive and time-consuming to conduct an intervention study in multiple European countries. Therefore, simulation using routine data can be used to estimate potential effects after safety of the intervention has previously been established in a previous clinical trial.

Second, we were not able to evaluate the safety of the implementation of the Feverkidstool in our simulation study as follow-up after ED visit was not available. The Feverkidstool proved to be safe in the intervention trial where safety was evaluated by secondary hospitalizations or antibiotic prescriptions, prolonged illness at Day 7 or complications. In low/intermediate-risk patients, implementation of the Feverkidstool did not change safety outcomes in the trial, whilst in high-risk patients fewer secondary

antibiotic prescriptions and prolonged duration of fever were observed. Safety is not likely to be different in EDs with lower or higher incidence of bacterial infections, since the clinical decision rule itself takes risk factors for bacterial pneumonia into account. Therefore, we assume that the Feverkidstool could be safely applied. Furthermore, Reilly *et al.*[28] suggest that the safety of a decision rule can be improved by a certain degree of non-compliance. In practice, physicians could overrule the recommendations of a decision rule due to clinical judgement. In our study, we simulated non-compliance by assuming that non-compliance would result in antibiotic prescriptions in low/intermediate-risk patients. This might overestimate antibiotic prescriptions for these patients.

Third, we simulated that all patients had equal probability on usage and compliance rates. We did not take into account that non-compliance might be related to higher predicted individual risks. Fourth, our inclusion criteria for fever (≥38.0°C) differed from that in the intervention trial (≥38.5°C). As temperature is a predictor in the Feverkidstool, this could have reflected a higher proportion of low/intermediate-risk patients in our cohort. It is unlikely that this has influenced calibration of the model as the population in which the Feverkidstool was developed was selected on a temperature of ≥38.0°C. Last, the Feverkidstool requires CRP levels to calculate individual risk scores and CRP measurement for febrile children varied widely (8%–90%) at European EDs.[21] To simulate the potential impact of the Feverkidstool, we imputed CRP values for patients without CRP measurement. We repeated analysis in complete cases of CRP level and found similar results, indicating that imputing CRP level did not influence our results.

The main strength of our study is that we simulated the impact of the Feverkidstool in a large European-wide cohort. Although EDs differed in case mix and baseline antibiotic prescriptions, we observed a reduction of antibiotics at every ED and significant reduction in nine EDs. This increases the generalizability of the potential effect of the Feverkidstool in young febrile children with respiratory symptoms. We believe our effect estimates to be representative for other EDs in Europe with comparable prescription rates and proportion of low/intermediate-risk patients. In the intervention trial, baseline antibiotic prescriptions were relatively low in the low/intermediate-risk group (17%) whereas in our study observed prescription rates were higher (overall 29.6%, range in EDs: 20.0%–44.4%). Our study showed that the potential antibiotic reduction is higher in EDs with higher baseline prescription rates. This agrees with a previous French study with a high baseline prescription rate (32%) where antibiotic prescriptions were significantly reduced by implementing antibiotic guidelines in paediatric respiratory tract infections.[2]

Simulation is an efficient method to collate evidence on impact of clinical decision rules, especially in situations when trials are not feasible. In addition, simulation introduces the possibility of changing assumptions in the models. We estimated the potential clinical impact on antibiotic prescription by applying the effect estimates on antibiotic prescription that were observed in the intervention trial, by varying usage and rates of compliance with the Feverkidstool, and in different age groups. Furthermore, cost-effectiveness analyses could be added to simulation studies[29] and simulation provides the ability to determine target values of usage and compliance rates before implementing the decision model. Next, simulation could also be used to estimate the potential effect on antibiotic prescription in other settings including primary care settings or low/middle-income countries with different baseline risks for bacterial infections.

As expected, our study showed that high usage and compliance were important to reach maximum effect of the Feverkidstool on antibiotic reduction.[28,30] Assuming a usage rate of 60% and a compliance rate of 90%, both frequently described in literature,[13–17] the Feverkidstool led to a prescription reduction of 10.0% (95% CI: 7.5%–12.4%). In practice, a high level of acceptance of CRP measurement and incorporating the clinical decision rule in the electronic hospital system will contribute to higher usage rates.[22]

The treatment decisions according to the Feverkidstool are targeted towards the low/intermediate-risk patients (withholding of antibiotics) whereas in high-risk patients, antibiotics were prescribed at the discretion of the physician. Since individual patient risks are only known after calculation of the Feverkidstool, all eligible patients were included in the intervention trial. As discussed by the authors,[12] the sample size was reached, but the proportion of low/intermediate-risk patients was lower than that expected in the power calculations. Subsequently, implementation of the Feverkidstool did not reduce overall antibiotic prescriptions, but did result in antibiotic reductions in the subgroup of children at low/intermediate risk. Instead of performing a new trial and exposing children to new risks, simulation is a good alternative to extrapolate trial data to populations with different risk profiles. In our simulation study, the proportion of low/intermediate-risk patients was higher (85%), based on the observed range across EDs of 70%–92%, than in the intervention study (58%). Consequently, our simulations in populations with predominance of low/intermediate risk resulted in reductions of overall antibiotic prescriptions. Our results indicate that reductions in antibiotic prescriptions can be achieved by ensuring a broad use of this tool. In addition, EDs with either high antibiotic prescription rates or many low-risk patients are likely to benefit the most from the implementation of the Feverkidstool.[3] Even in EDs with lower prescription rates, ensuring high usage of and compliance with the Feverkidstool has a substantial effect on antibiotic prescription.

The risk threshold of 10% in the intervention trial was chosen according to previous literature.[8,9,12] An appropriate threshold should balance the potential harm of undertreating bacterial LRTIs and the benefit of reducing unnecessary antibiotic prescriptions. Physicians may consider accepting a higher risk threshold of 15% if adequate safety-netting is provided.

The Feverkidstool is broadly validated for all paediatric age groups.[9,11] Since viral infections have higher incidence in younger children, the intervention trial was performed in children aged <5 years. Although the safety of withholding antibiotic prescriptions has not yet been established in children aged >5 years at low/intermediate risk for suspected LRTIs, our study shows that implementation of the Feverkidstool has the potential to reduce antibiotic prescriptions in this group. Future studies should be performed in older children to address safety and actual effect on antibiotic prescription.

Differences between European EDs, including acceptance of CRP measurement, should be taken into account when implementing a new strategy for antibiotic reduction in Europe.[21,22] Furthermore, a clinical decision rule could also aid in guiding decisions regarding appropriateness of antibiotic agents and prescription mode. Future research should focus on identifying local

facilitators and barriers for the implementation of this clinical decision rule to achieve maximal uptake. In addition, the Feverkidstool should be validated in children with comorbidity.

### *Conclusions*

Based on routine clinical data, we modelled the potential effect of implementation of the Feverkidstool, a clinical decision rule advising physicians whether or not to start antibiotic treatment in children with suspected LRTIs. Our simulation study showed that the Feverkidstool has the potential to reduce antibiotic prescription from 33.5% to 24.1% at European EDs. Both usage and compliance with the treatment advice influence the potential effect on antibiotic prescription. In addition, simulation predicted a significant reduction of antibiotics at nine participating EDs. EDs with both higher antibiotic prescription rates and many low/intermediate-risk patients are likely to benefit more from this decision rule. Therefore, the Feverkidstool could contribute to reducing antibiotic prescriptions for LRTIs in Europe.

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## Transparency declarations

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### *Author contributions*

Conceptualization: N.N.H., J.H.L.W., D.N., D.B., U.v.B., E.D.C., I.E., M.E., M.v.d.F., R.d.G., J.H., B.K., M.L., E.L., I.M., F.M.-T., R.N., M.P., I.R.C., M.T., S.Y., D.Z., W.Z., C.L.V., R.O. and H.A.M. Data curation: N.N.H., D.B., U.v.B., E.D.C., I.E., M.E., M.v.d.F., R.d.G., J.H., B.K., M.L., E.L., I.M., F.M.-T., R.N., M.P., I.R.C., M.T., D.Z., W.Z. and H.A.M. Formal analysis: N.N.H., J.H.L.W., D.N., R.O. and H.A.M. Methodology: N.N.H., J.H.L.W., D.N., D.B., U.v.B., E.D.C., M.E., M.v.d.F., R.d.G., J.H., B.K., M.L., E.L., F.M.-T., R.N., M.P., I.R.C., M.T., S.Y., D.Z., W.Z., C.L.V., R.O. and H.A.M. Supervision: H.A.M. Visualization: N.N.H. and J.H.L.W. Writing—original draft: N.N.H. and J.H.L.W. Writing—review and editing: D.N., D.B., U.v.B., E.D.C., I.E., M.E., M.v.d.F., R.d.G., J.H., B.K., M.L., E.L., I.M., F.M.-T., R.N., M.P., I.R.C., M.T., S.Y., D.Z., W.Z., C.L.V., R.O. and H.A.M. Guarantors (N.N.H., J.H.L.W. and H.A.M.) accept full responsibility for the work and/or the conduct of the study, verified the underlying data and controlled the decision to publish. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

## Data sharing

An anonymized dataset containing individual participant data is available in a public data repository: https://data.hpc.imperial.ac.uk/resolve/?doi=7809. DOI: 10.14469/hpc/7809. For enquiries to obtain the full dataset, please contact the data manager of the PERFORM consortium (Tisham.de08@imperial.ac.uk).

## Supplementary data

Tables S1 to S7, Figure S1 and Supplementary information regarding PERFORM (Text S1) are available as Supplementary data at *JAC* Online.

## References

**1** Harris M, Clark J, Coote N *et al.* British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax* 2011; **66**: ii1–23.

**2** Angoulvant F, Skurnik D, Bellanger H *et al.* Impact of implementing French antibiotic guidelines for acute respiratory-tract infections in a paediatric emergency department, 2005-2009. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 1295–303.

**3** van de Maat J, van de Voort E, Mintegi S *et al.* Antibiotic prescription for febrile children in European emergency departments: a cross-sectional, observational study. *Lancet Infect Dis* 2019; **19**: 382–91.

**4** Tacconelli E, Sifakis F, Harbarth S *et al.* Surveillance for control of antimicrobial resistance. *Lancet Infect Dis* 2018; **18**: e99–106.

**5** Cassini A, Hogberg LD, Plachouras D *et al.* Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; **19**: 56–66.

**6** Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Arch Dis Child* 2009; **94**: 724–8.

**7** McGinn TG, Guyatt GH, Wyer PC *et al.* Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. *JAMA* 2000; **284**: 79–84.

**8** van de Maat J, Nieboer D, Thompson M *et al.* Can clinical prediction models assess antibiotic need in childhood pneumonia? A validation study in paediatric emergency care. *PLoS One* 2019; **14**: e0217570.

**9** Nijman RG, Vergouwe Y, Thompson M *et al.* Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. *BMJ* 2013; **346**: f1706.

**10** de Vos-Kerkhof E, Nijman RG, Vergouwe Y *et al.* Impact of a clinical decision model for febrile children at risk for serious bacterial infections at the emergency department: a randomized controlled trial. *PLoS One* 2015; **10**: e0127620.

**11** Irwin AD, Grant A, Williams R *et al.* Predicting risk of serious bacterial infections in febrile children in the emergency department. *Pediatrics* 2017; **140**: e20162853.

**12** van de Maat JS, Peeters D, Nieboer D *et al.* Evaluation of a clinical decision rule to guide antibiotic prescription in children with suspected lower respiratory tract infection in the Netherlands: a stepped-wedge cluster randomised trial. *PLoS Med* 2020; **17**: e1003034.

**13** Geurts DH, Vos W, Moll HA *et al.* Impact analysis of an evidence-based guideline on diagnosis of urinary tract infection in infants and young children with unexplained fever. *Eur J Pediatr* 2014; **173**: 463–8.

**14** Roukema J, Steyerberg EW, van der Lei J *et al.* Randomized trial of a clinical decision support system: impact on the management of children with fever without apparent source. *J Am Med Inform Assoc* 2008; **15**: 107–13.

**15** Demonchy E, Dufour JC, Gaudart J *et al*. Impact of a computerized decision support system on compliance with guidelines on antibiotics prescribed for urinary tract infections in emergency departments: a multicentre prospective before-and-after controlled interventional study. *J Antimicrob Chemother* 2014; **69**: 2857–63.

**16** McGinn TG, McCullagh L, Kannry J *et al*. Efficacy of an evidence-based clinical decision support in primary care practices: a randomized clinical trial. *JAMA Intern Med* 2013; **173**: 1584–91.

**17** Tra J, van der Wulp I, Appelman Y *et al*. Adherence to guidelines for the prescription of secondary prevention medication at hospital discharge after acute coronary syndrome: a multicentre study. *Neth Heart J* 2015; **23**: 214–21.

**18** Geurts D, de Vos-Kerkhof E, Polinder S *et al*. Implementation of clinical decision support in young children with acute gastroenteritis: a randomized controlled trial at the emergency department. *Eur J Pediatr* 2017; **176**: 173–81.

**19** Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Ann Emerg Med* 1999; **33**: 437–47.

**20** Sachs MC, Sjölander A, Gabriel EE. Aim for clinical utility, not just predictive accuracy. *Epidemiology* 2020; **31**: 359–64.

**21** Hagedoorn NN, Borensztajn DM, Nijman R *et al*. Variation in antibiotic prescription rates in febrile children presenting to emergency departments across Europe (MOFICHE): a multicentre observational study. *PLoS Med* 2020; **17**: e1003208.

**22** Borensztajn D, Yeung S, Hagedoorn NN *et al*. Diversity in the emergency care for febrile children in Europe: a questionnaire study. *BMJ Paediatr Open* 2019; **3**: e000456.

**23** Simon TD, Cawthon ML, Stanford S *et al*. Pediatric medical complexity algorithm: a new method to stratify children by medical complexity. *Pediatrics* 2014; **133**: e1647–54.

**24** Advanced Life Support Group. *Advanced Paediatric Life Support: The Practical Approach*. Wiley, 2011.

**25** Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. *Pediatr Infect Dis J* 1997; **16**: 735–47.

**26** Hirji KF, Fagerland MW. Calculating unreported confidence intervals for paired data. *BMC Med Res Methodol* 2011; **11**: 66.

**27** Wallace E, Smith SM, Perera-Salazar R *et al*. Framework for the impact analysis and implementation of clinical prediction rules (CPRs). *BMC Med Inform Decis Mak* 2011; **11**: 62.

**28** Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med* 2006; **144**: 201–9.

**29** Smits M, Dippel DWJ, Nederkoorn PJ *et al*. Minor head injury: CT-based strategies for management - a cost-effectiveness analysis. *Radiology* 2010; **254**: 532–40.

**30** Reilly BM, Evans AT, Schaider JJ *et al*. Impact of a clinical decision rule on hospital triage of patients with suspected acute cardiac ischemia in the emergency department. *JAMA* 2002; **288**: 342–50.