Childhood pneumonia

Clinical decision support in the emergency department

Josephine van de Maat

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Chapter 1

General introduction

The burden of childhood pneumonia

Pneumonia is an infection of the alveoli in the lower respiratory tract. Together with bronchiolitis (infection of the bronchioles), pneumonia forms the biggest share of lower respiratory tract infections (RTI) in children. Pneumonia mostly presents with fever, cough and/or respiratory distress. Even though the term pneumonia is often used as a synonym of bacterial infection, a large proportion of the lower RTIs in young children are of viral origin. In primary care, out of all febrile children, less than 1% has a bacterial infection.[1] In the emergency department (ED) this proportion goes up to 10 – 15%, of whom 30-70% is diagnosed with a pneumonia.[2-5]

Worldwide, lower RTIs are the leading cause of death in children after the neonatal period and under the age of five. Each year, an estimated 800,000 children under five die worldwide due to lower RTIs (mortality rate 119/100,000 per year).[6,7] There are large disparities globally in pneumonia mortality, with the highest burden of disease in the global south. In high-income countries the mortality rate has dropped dramatically over the past decades (Figure 1).[8] This is mainly due to the introduction of antibiotics, improved hygiene and access to healthcare, and more recently the introduction of vaccination against Haemophilus influenzae type b (Hib) since the 1990s and against pneumococcal disease (PCV, Pneumococcal Conjugate Vaccine) since the years 2000.[6,9,10] Currently, mortality rate due to lower RTIs in western Europe is 1.7/100,000.[6]

Despite these relatively low mortality rates, lower RTIs in children still cause a high burden of disease in Europe. Fever and respiratory complaints are the main reason for children to be brought to a doctor and account for 30-50% of all paediatric ED visits.[11-13] In children under five, lower RTIs are responsible for >100.000 primary care consultations and >7.000 ED visits in the Netherlands annually.[14,15] A substantial proportion of those children need hospital admission, posing a burden on the child and its family, but also to healthcare in terms of costs.

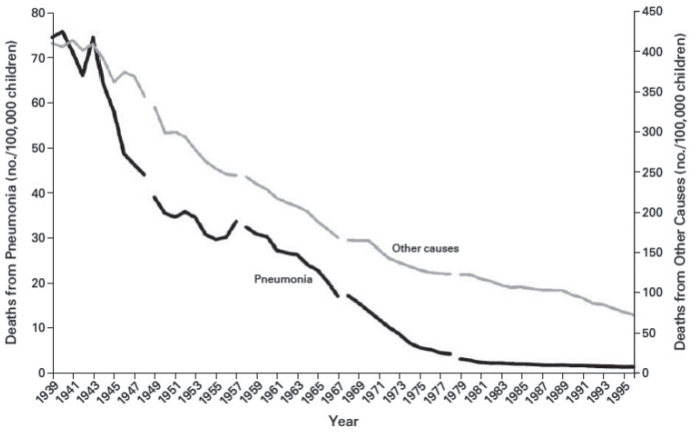

Figure 1. Deaths from pneumonia and from other causes in childhood. Data from the United States, trend is comparable to western Europe.[8]

Antimicrobial resistance on the rise

The introduction of antibiotics was the main driver of the reduction in pneumonia mortality worldwide. However, the use of antibiotics also has its downsides. Misuse and overuse of antibiotics fuels antimicrobial resistance (AMR) that threatens the health of the general public.[16,17] A recent study has shown that resistant bacteria in the European Union region were responsible for >27,000 deaths in 2015, a number that has more than doubled since 2007.[18] Especially in eastern Europe, bacteria become more and more resistant to commonly used antibiotics. This calls for urgent action, and the World Health Organization (WHO) and European Commission have declared AMR as a top public health threat.[17,19] To reduce inappropriate antibiotic use, antibiotic stewardship programmes have been launched worldwide, but few of them include the ED.[20] Most studies on antibiotic prescription in febrile children have focused on primary care or in-hospital settings.[21,22]

Management of children in the ED

The management of children in the ED usually follows different steps, each with its key decision-makers (Figure 2). First, parents bring their child into the ED for medical consultation, in the Netherlands mostly after referral by a general practitioner (GP). Next, triage is performed to determine the level of urgency of the child's illness, usually by a nurse. A nurse also does a first clinical assessment, including the measurement of vital signs. Then a doctor takes the clinical history, examines the child and may decide to perform additional diagnostic tests. Based on all the obtained information, the doctor decides on treatment

and disposition of the child. Before leaving the ED, discharge information is provided to the parents, including instructions on when to return to the hospital. Even though many of these decisions are made jointly between the healthcare workers and parents, the main responsibility of the decisions varies throughout the process.

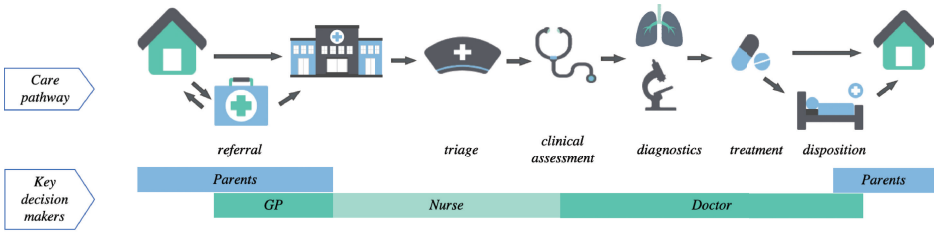

Figure 2. Care pathway and key decision makers in the paediatric ED.

Identifying children in need of antibiotics

Given the dual risk of bacterial pneumonia on the one hand and of antimicrobial resistance on the other hand, it is crucial to identify and treat only those children that really need antibiotic treatment. However, this is very difficult in clinical practice. Children often present with symptoms like fever and cough, which are not specific for viral or bacterial disease. Other clinical features like vital signs can help identify severe illness, but are not specific for bacterial causes of disease either. Multiple studies have shown the lack of diagnostic accuracy of clinical signs and symptoms to identify bacterial infections, including pneumonia.[1,4,23]

For a long time, the chest X-ray was considered the gold standard to diagnose bacterial pneumonia. However, more recent evidence revealed its limitations, especially the high inter-observer variability and the inability to distinguish viral from bacterial causes of disease.[24,25] Therefore, current guidelines for community-acquired pneumonia in children do not recommend routine use in most children in the outpatient setting. The British Thoracic Society (BTS) and the Infectious Diseases Society of America (IDSA) advise to restrict the use of a chest X-ray to children with moderate to severe signs and symptoms of pneumonia, who are at risk of developing complications.[26,27] Both guidelines were released in 2011, and the Dutch guideline for fever in children followed the same advice (published in 2013).[28]

There are several other diagnostic tools available, but they all have their limitations.[29] Sputum is difficult to obtain in children, so bacterial sputum cultures are not feasible. Blood cultures are not useful, because the prevalence of bacteraemia in children with pneumonia is very low.[30] Viral PCR testing is mostly performed on samples of the upper airways like the

nasopharynx. These results can support the diagnosis of viral disease, but the connection between the flora of the upper and lower airways is unclear and bacterial co-infection cannot be excluded.[31] The Dutch guideline for fever in children only recommends routine viral testing in the influenza or Respiratory Syncytial Virus (RSV) season.[28] Lastly, biomarkers identifying the host-response to infection are available and used in children suspected of a pneumonia.[32] The most common biomarkers used for this purpose are C-reactive protein (CRP), and – less frequently – procalcitonin.[33,34] However, both have limited diagnostic accuracy in identifying bacterial disease. New markers are being developed, but not yet available in routine clinical practice.[35-37]

Outcome-based research

The difficulty of diagnosing bacterial infections can lead to misclassification of diagnoses, reducing the comparability of studies on febrile children.[38] To avoid this, some authors have argued to focus research more on the outcomes or consequences of the disease than on the diagnosis itself.[39] In other words, they propose to shift from trying to identify the causative pathogen to focusing on the consequences of the infection in clinical practice. These consequences are 1) does this child require antibiotic treatment? and 2) does this child need to be hospitalized? (Figure 3) In the case of RTIs: a child with a bacterial pneumonia can often be managed with antibiotics in the outpatient setting, while children with bronchiolitis do not need antibiotic treatment, but may even need supportive care at an intensive care unit.[39]

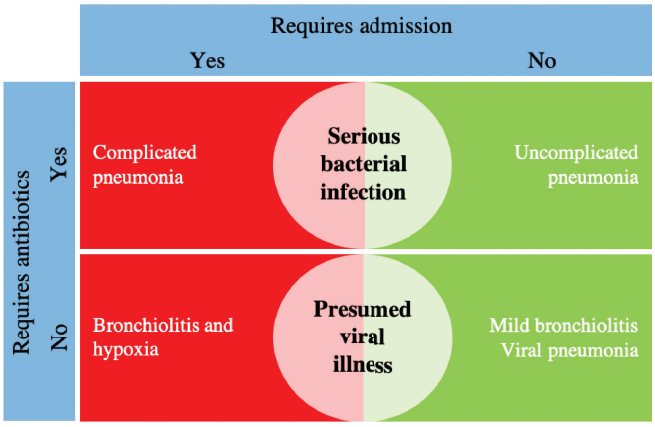

Figure 3. Classification of diagnosis and management of fever and RTIs, adapted from Irwin et al.[39]

Clinical decision support for fever and pneumonia

In order to aid physicians in managing children with fever and RTIs, multiple decision support tools exist. Mostly common are clinical guidelines, that are available for fever in general [28,40], and for pneumonia in particular.[26,27] Even though these guidelines provide useful recommendations for daily practice, they are based on studies of varying degrees of evidence and on expert opinion. Moreover, they provide rather general advice that often leaves room for interpretation, and they do not provide decision support at the individual patient level. Another form of decision support can be provided by clinical prediction models, that provides a risk prediction at the individual level. In contrast to the development of clinical guidelines, there are strict methodological steps in the development of prediction models, as mentioned in Table 1.[41] Across the field of medical research, many prediction models are derived, but few of them are validated and even fewer are translated into decision rules and implemented in daily clinical practice.[42,43] Several prediction models exist for diagnosing childhood pneumonia, among others the Feverkidstool that has been derived and validated by Nijman et al.[2] This prediction model combines clinical signs and symptoms and a CRP-level to predict the probability that a child has a pneumonia, another serious bacterial infection (SBI), or no bacterial infection. The model has been externally validated in different settings in The Netherlands and the United Kingdom (step 3 in Table 1), showing good diagnostic accuracy for both pneumonia and other SBIs (area under the receiving operator curve 0.83-0.85 for pneumonia and 0.81 for other SBI).[3,44]

Table 1. Steps of development and evaluation of clinical prediction rules. Cited from Reilly et al. [41]

Level of evidence	Definitions	Implications for clinicians
1. Derivation of prediction rule	Identification of predictors using multivariate model	Needs validation and further evaluation before using clinically in actual patient care
2. Narrow validation of prediction rule	Verification of predictors when tested prospectively in one setting; blinded assessment of outcomes	Needs validation in varied settings; may use predictions cautiously in patients similar to sample studied
3. Broad validation of prediction rule	Verification of predictive model in varied settings with wide spectrum of patients and physicians	Needs impact analysis; may use predictions with confidence in their accuracy
4. Narrow impact analysis of prediction rule used as decision rule	Prospective demonstration in one setting that use of prediction rule improves physicians' decisions (quality or cost-effectiveness of patient care)	May use cautiously to inform decisions in settings similar to that studied
5. Broad impact analysis of prediction rule used as decision rule	Prospective demonstration in varied settings that use of prediction rule improves physicians' decisions for wide spectrum of patients	May use in varied settings with confidence that its use will benefit patient care quality or effectiveness

Decision support of parents after ED discharge

In addition to healthcare providers, parents are key players in the decisions on managing children with fever and RTIs (Figure 2). This starts with the decision to care for the child at home or to seek medical attention and when to do so, but this decision process continues after an ED visit. Given the difficulty of distinguishing bacterial pneumonia from self-limiting viral illness, uncertainty about the diagnosis often remains after evaluation of the febrile child in the ED. It is therefore crucial that parents are supported in their decisions on how to manage their child at home and on when to return to the ED. However, parents often have difficulty in recognizing specific alarming symptoms in their febrile child [45], and have poor understanding of clinical information and discharge instructions provided by the ED staff.[46,47] In order to reduce unnecessary ED visits, but also to prevent missing serious illness, parents need clear discharge information on how to monitor recovery or deterioration of their child's illness after the ED visit.[48,49]

Aims of this thesis

This thesis aims to evaluate and improve clinical decision-making for the diagnosis and treatment of childhood pneumonia in the ED. In particular, it aims to answer the following research questions:

Variability in management of childhood pneumonia in the emergency department

1. What is the current practice in diagnosis and treatment of children with fever and respiratory tract infections in the European emergency department, in particular regarding the measurement of vital signs, performance of chest X-rays and antibiotic prescription?
2. Can we explain variability in antibiotic prescriptions for respiratory tract infections by differences in the population?

Supporting treatment decisions for childhood pneumonia

3. Can clinical prediction models guide antibiotic treatment decisions for childhood pneumonia?
4. Can we safely reduce antibiotic prescription in children under five suspected of a lower respiratory tract infection in the emergency department, by implementing the Feverkidstool as a clinical decision rule?
5. Can we improve the diagnosis of serious bacterial infections if we update the Feverkidstool by replacing CRP by new biomarkers?

6. What are parents' views on, and experiences of managing their febrile child and what are their behaviour and needs when in search of information about fever?
7. How do parents evaluate a developed hospital discharge information package about fever in children?

Outline

The first part of this thesis describes current variability in the management of children with fever and/or suspected lower RTIs in the ED. The NICE guideline for fever in children under five recommends to measure four vital signs routinely in all febrile children. In **chapter 2.1** we describe variability in measuring vital signs in febrile children in European EDs, and the adherence to specific NICE guideline recommendations. For this analysis we use a population of febrile children from 28 European EDs within the REPEM (Research in European Pediatric Emergency Medicine) network. In **chapter 2.2** we describe the use of chest X-ray in diagnosing pneumonia in children, and the influence of the chest X-ray on antibiotic prescription. For this purpose, we use the usual care data of a multicentre trial in children under five in eight EDs in The Netherlands (STRAP trial). In **chapter 2.3**, we use the international REPEM population to quantify and explain the variability in antibiotic prescription in European EDs.

In the second part of this thesis we investigate the role of clinical prediction models in supporting decisions on antibiotic treatment for childhood pneumonia. In **Chapter 3.1** we review the available clinical prediction models for childhood pneumonia, including the Feverkidstool. Most models are based on chest X-ray as the reference standard. However, since this is no longer used as a gold standard, we validate the available prediction models for a clinical diagnosis of pneumonia. We also explore possible thresholds for supporting treatment decisions to be used in clinical practice. **Chapter 3.2** presents the results of a stepped wedge, cluster randomized trial in which the Feverkidstool was used to guide antibiotic treatment in children under five suspected of a lower RTI in the ED (STRAP trial). In **chapter 3.3** the economic impact of the Feverkidstool is described, also providing cost data of children with lower RTIs in the ED in general. In **chapter 3.4** we update the Feverkidstool by replacing CRP with the ImmunoXpert, a host-protein based assay combining CRP, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and interferon γ induced protein-10 (IP-10).

The last part of this thesis focuses on the role of parents in the management of febrile children. In **chapter 4.1** we use qualitative research methods to explore parents' views on and experiences of managing their febrile child. We also assess their behaviour and needs when in search of information about fever. Based on this, we develop and evaluate a hospital discharge information package about fever in children.

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Chapter 2.

Variability in management of childhood pneumonia in the emergency department

Chapter 2.1.

Measuring vital signs in febrile children at the emergency department: an observational study on adherence to the NICE recommendations in Europe.

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ABSTRACT

Vital signs can help clinicians identify children at risk of serious illness. The NICE guideline for fever in under-fives recommends a routine measurement of temperature, heart rate, capillary refill and respiratory rate in all febrile children visiting the Emergency Department (ED). This study aims to evaluate the measurement of paediatric vital signs in European EDs, with specific attention to adherence to this NICE guideline recommendation. In a prospective observational study we included 4560 febrile children under 16 years from the ED of 28 hospitals in 11 European countries (2014–2016). Hospitals were academic (n = 17), teaching (n = 10) and non-teaching (n = 1) and ranged in annual paediatric ED visits from 2700 to 88,000. Fifty-four percent were male, their median age was 2.4 years (IQR 1.1–4.7). Temperature was measured most frequently (97%), followed by capillary refill (86%), heart rate (73%), saturation (56%) and respiratory rate (51%). In children under five (n=3505), a complete measurement of the four NICE-recommended vital signs was performed in 48% of patients. Children under one year of age, those with an urgent triage level and with respiratory infections had a higher likelihood of undergoing complete measurements. After adjustment for these factors, variability between countries remained.

Conclusion: Measuring vital signs in children with fever in the ED occurs with a high degree of practice variation between different European hospitals, and adherence to the NICE recommendation is moderate. Our study is essential as a benchmark for current clinical practice, in order to tailor implementation strategies to different European settings.

INTRODUCTION

Fever is the most common reason for children to be brought to an emergency department (ED)[1-3], with causes ranging from self-limiting illnesses of childhood to serious bacterial infections (SBIs) that can prove fatal.[3-5] Vital signs can help clinicians identify children at risk of serious illness. Even though the level of evidence for the diagnostic accuracy of vital signs is varying, their importance is widely acknowledged.[6] Vital signs form the basis of Paediatric Early Warning Scores (PEWS) that are widely used to monitor disease severity of children in the inpatient setting.[7] Moreover, they are included in several prediction models for serious infections and in disease-specific guidelines for the ED setting.[3,8-12] The NICE guideline for the assessment and initial management of fever in children under five recommends a routine measurement of temperature, heart rate, capillary refill and respiratory rate in all children presenting to the ED with a fever.[13] These recommendations have been adopted throughout a large number of European hospitals.

Not measuring vital signs may pose the patient at risk of underestimating the severity of illness and may delay appropriate treatment.[14] From adult research and single-country studies we know that incomplete and inaccurate recording of vital signs is common.[15-17] This problem may be even larger in Europe, given the diversity of the countries, cultures and healthcare systems. However, international data on recording of vital signs across Europe in children are lacking.[18] Information on the measurement of vital signs is crucial in order to fuel research on serious illness and to target quality improvement initiatives in paediatric emergency medicine. This research aims to evaluate the current practice of measuring vital signs in febrile children in European EDs and, more specifically, the level of adherence to the NICE guideline recommendation to routinely measure four distinct vital signs.

METHODS

Study design and population

We performed a prospective observational study in 28 EDs in 11 European countries, including patients under the age of 16 and with a fever as their presenting complaint. Children were excluded if they presented to the ED repeatedly for the same problem within 7 days, if they were treated with antibiotics in the 7 days before the ED visit, or if they had a documented allergy to antibiotics. For the current study, children with comorbidities were also excluded, as disease-specific characteristics may influence their management. In the whole population, we evaluated the measurement of vital signs. In children under five, we assessed the adherence

to the recommendations to measure four distinct vital signs from the NICE guideline 'Fever in under 5s: assessment and initial management'.[13]

Data collection

Data collection took place between October 2014 and February 2016 within the network of Research in European Pediatric Emergency Medicine (REPEM). Detailed methods have been published earlier.[19] In short, all participating 28 EDs recorded medical information for all attending children with fever for one random day each month. We recorded general characteristics of patients (age, sex, weight, height, comorbidities), vital signs (heart rate, respiratory rate, temperature, oxygen saturation, capillary refill time) and information regarding diagnosis and management. Data were extracted from routine patient records, and filled in on an electronic study case report form (CRF) by the local investigator after the sampling day (Electronic Supplementary Material 1). Comorbidities and diagnoses were recorded according to pre-specified categories. We neither used ICD-codes for the recording of diagnoses, nor had we access to data after the ED visit. Consequently, 'diagnosis' in this manuscript refers to a presumed diagnosis at ED discharge. All items in the CRF were mandatory to fill in, with the option to choose 'unknown'. Unknown values on vital signs were seen as 'not measured', and were therefore considered to be outcomes rather than omissions. Local investigators were aware of the sampling days and the general scope of the study as a registry of febrile children, but vital sign measurement was not known as a specific point of interest. Hospital information was collected using a survey, including questions on guideline use. We collected data on hospital setting (inner city/rural/mixed), hospital type (academic/teaching/non-teaching), triage system, and number of annual paediatric ED visits, similar to other studies on the organization of care (Electronic Supplementary Material 2).[20] Setting reflects the population in the catchment area of the hospital. Academic hospitals are connected to a university, teaching hospitals are non-university hospitals that provide training for paediatrics residents, non-teaching hospitals do not provide training of residents.

Definitions

Not every study hospital used the same triage system, but they all classified children according to a five-point scale, ranging from 'non-urgent' to 'immediate', making comparisons possible. Owing to the small number of cases, patients in the 'immediate' and 'very urgent' categories were grouped together. Tachycardia and tachypnoea were defined according to the advanced pediatric life support (APLS) guideline.[21] Fever was defined as temperature ≥38 °C, hypoxia as peripheral oxygen saturation level of ≤ 94%. Crowding of the ED was defined for each hospital according to their number of total paediatric ED visits on the sampling day (less than usual/as usual/more than usual). We defined a usual number of total visits as the interquartile

range of the number of total visits across the different sampling days per hospital. If on a sampling day the number of total visits was lower than the 25th percentile for that hospital, crowding was less than usual, if the number was higher than the 75th percentile, the ED was more crowded than usual.

Adherence to the NICE guideline was based on the following indicator: "*Measure and record temperature, heart rate, respiratory rate and capillary refill time as part of the routine assessment of a child with fever.*".[13] Adherence to the NICE guideline was defined as the complete measurements of those four vital signs in children under 5 years old.

Statistical analysis

We used descriptive analyses to evaluate the frequency of measurement for all of the available vital signs in the study population. We examined practice variations between countries, age groups, triage levels and diagnoses, visualizing the measurement of vital signs by heat maps. We used diagnosis in these analyses as a proxy of presenting complaint (next to the fever) and suspicion of severity, assuming that children with RTIs would present with respiratory symptoms, enteric infections with vomiting or diarrhoea and that children with fever without source, urinary tract infections and sepsis/meningitis mostly present without specific symptoms but with a higher suspicion of invasive infections. We compared the frequency of detecting abnormal vital signs between countries that frequently measured vital signs and countries that measured them less often.

In assessing adherence to the NICE guideline, we measured the frequency of complete measurements in children under five from all hospitals that used the NICE recommendations. We tested the influence of age, triage level, diagnosis and crowding of the ED on adherence using a multilevel logistic regression model that included hospital as a random variable. Analyses were performed using SPSS (IBM, version 24) and R (version 3.5.2).

RESULTS

Population characteristics

In total, 5255 children were included in the complete cohort, all presenting with fever and without prior antibiotic treatment or repeated ED visits. In the current study, we included 4560 children. Exclusion was mostly because of comorbidities (Fig. 1). Of the included children, 53.8% were male and the median age was 2.4 years (interquartile range 1.1–4.7). Table 1 shows their baseline characteristics and provides information regarding patients' way of referral and follow-up. Baseline characteristics of children with comorbidities has been

published earlier.[19] In general, these children were more ill and older than children without comorbidities. Of the 28 participating hospitals, 17 were academic hospitals, 10 teaching hospitals and one non-teaching hospital (Table 2). They varied from inner city hospitals (n = 17) to regional (n = 2) and mixed hospitals (n = 9) and their number of annual paediatric ED visits ranged from 2700 to 88,000. Most hospitals used a local triage system (n = 8) or the Manchester Triage System (n = 7, Table 2). All except the Spanish hospitals used the recommendation to routinely measure vital signs as mentioned in the NICE guideline.

Fig. 1 Flowchart of inclusion

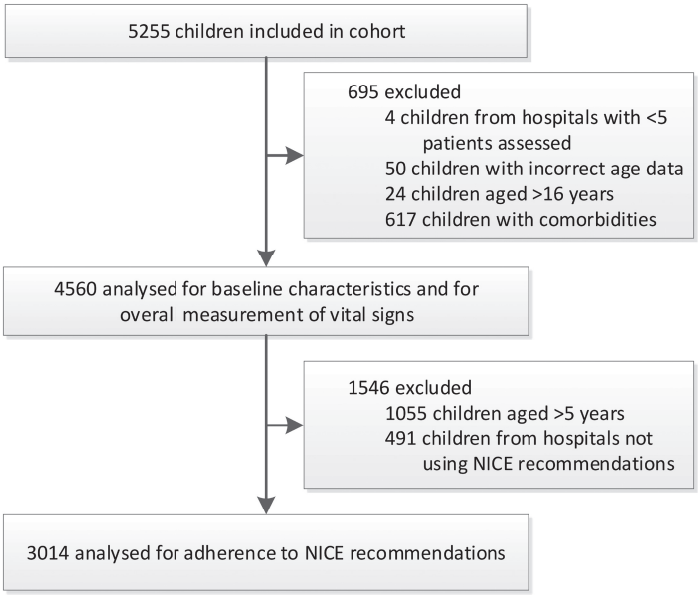

Table 1. Baseline characteristics of the population, n = 4560

General characteristics	n/N (%)[a]
Male sex	2451/4557 (53.8%)
Age in years[b]	2.4 (1.1–4.7)
Season	
- Spring	1110/4560 (24.3%)
- Summer	766/4560 (16.8%)
- Autumn	1024/4560 (22.5%)
- Winter	1660/4560 (36.4%)
Way of referral	
- General practitioner	395/4524 (8.7%)
- Self	3966/4524 (87.7%)
- Other healthcare professional	163/4524 (3.6%)
Triage level	
- Immediate or very urgent	197/3850 (5.1%)
- Urgent	1042/3850 (27.1%)
- Standard	1866/3850 (48.5%)
- Non-urgent	745/3850 (19.4%)
Abnormal vital signs	
Fever (temperature ≥ 38 °C)	2403/4435 (54.2%)
Tachycardia[c]	1138/3341 (34.1%)
Tachypnoea[c]	665/2333 (28.5%)
Hypoxia (oxygen saturation ≤ 94%)	85/2567 (3.3%)
Prolonged capillary refill (> 3 s)	67/4560 (1.5%)
Disposition	
- Discharged home	4035/4559 (88.5%)
- Observation unit <24h	187/4559 (4.1%)
- Admitted to ward	321/4559 (7.0%)
- Admitted to ICU	11/4559 (0.2%)

Footnote:

[a] *Unless stated otherwise*

[b] *Median (interquartile range)*

[c] *According to APLS guidelines*

Table 2. Hospital information

Hospital	Country (code)	n	Annual PED visits	Type	Setting	Responsible specialist	Triage system	NICE recommendations on measurement of vital signs in use?
Aarhus Universitetshospital, Skejby	Denmark (DK)	24	5000	Academic	Mixed	Paediatrician	Local/National	Yes[a]
Hopital Antoine Béclère, Paris	France (FR)	53	25,000	Academic	Inner city	U	U	Yes[a]
Hôpital Mère-Enfant, Nantes		118	> 25,000	Academic	Inner city	Paediatrician	Local/National	
Hôpital Necker-Enfants malades, Paris		285	66,000	Academic	Inner city	PEM specialist	Local/National	
Hopital Robert Debre, Paris		384	88,000	Academic	Inner city	Paediatrician	U	
Roger Salengro Hospital, Lille		86	25,000	Teaching	Inner city	PEM specialist	MTS	
Heim Pal Children's Hospital, Budapest	Hungary (HU)	111	30,000	Teaching	Mixed	Paediatrician	CTAS	Yes[a]
Meyer University Children's Hospital, Florence	Italy (IT)	160	42,000	Academic	Inner city	Paediatrician	Local/National	Yes[b]
Ospedale dei Bambini, Azienda Ospedaliera Spedali Civili, Brescia		182	36,500	Academic	Mixed	Paediatrician	Local/National	
University Hospital, Padova		104	25,000	Academic	Inner city	Paediatrician	Local/National	
ErasmusMC – Sophia, Rotterdam	The Netherlands (NL)	60	4000	Academic	Inner city	Paediatrician	MTS	Yes[b]
Flevoziekenhuis, Almere		19	5000	Teaching	Mixed	Paediatrician	MTS	
Maasstad Ziekenhuis, Rotterdam		28	3500	Teaching	Inner city	Paediatrician	MTS	
Reinier de Graaf, Delft		29	2643	Teaching	Mixed	Paediatrician	MTS	
Sint Franciscus Ziekenhuis, Rotterdam		25	2700	Teaching	Inner city	Paediatrician	MTS	
Centro Hospitalar de Leiria, Leiria	Portugal (PT)	201	46,000	Teaching	Mixed	Paediatrician	Local/National	Yes[b]
Lisbon Medical Academic Center (Hospital de Santa Maria), Lisboa		282	50,000	Academic	Inner city	Paediatrician	Local/National	
Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra		215	60,000	Academic	Inner city	Paediatrician	CTAS	

Table 2. (continued)

Hospital	Country (code)	n	Annual PED visits	Type	Setting	Responsible specialist	Triage system	NICE recommendations on measurement of vital signs in use?
Emergency Children's Hospital, Cluj Napoca	Romania (RO)	168	9400	Teaching	Rural	Paediatrician or PEM	ESI	Yes[b]
Tirgu Mures Emergency Clinical County Hospital, Tirgu Mures		114	16,000	Academic	Inner city	Paediatrician	ESI	
Cruces University Hospital Bilbao, Basque country	Spain (ES)	230	53,000	Academic	Inner city	PEM specialist	CTAS	No
Hospital de Mendaro, Mendaro (Guipúzcua)		60	7160	Non-teaching	Rural	U	U	
Hospital Universitario Rio Hortega, Valladolid		248	24,000	Teaching	Mixed	PEM specialist	PAT	
San Agustín University Hospital, Linares, Jaén		93	U	Teaching	Mixed	Paediatrician	U	
University Hospital, Geneva	Switzerland (CH)	230	25,500	Academic	Inner city	PEM specialist	CTAS	Yes[a]
Children's Hospital of Zurich, Zurich		198	37,000	Academic	Inner city	Emergency physician	ATS	
Cukurova University Medical Faculty Balcali Hospital, Adana	Turkey (TK)	708	20,000	Academic	Mixed	PEM specialist	none	Yes[b]
St Mary's Hospital, London	United Kingdom (UK)	145	27,000	Academic	Inner city	PEM specialist	MTS	Yes[b]

Footnote:

[a] recommended in local triage or ED guideline

[b] recommended in NICE or NICE-based fever guideline

PED = paediatric emergency department; PEM = paediatric emergency medicine; U = unknown; MTS = Manchester Triage System; CTAS = Canadian Triage and Acuity Scale; ESI = Emergency Severity Index; PAT = Pediatric Assessment Triangle; ATS = Australasian Triage Scale

Overall measurement of vital signs and per country

The measurement of vital signs occurred in varying degrees, both when comparing the different vital signs with each other and across participating countries. Overall, temperature was measured most frequently (97%, 4435/4560, 95% confidence interval 97–98%), ranging between countries from 70% (78/111) in Hungary to 100% in Denmark and England (n = 24 and n = 145 respectively). Capillary refill was next (86%, 85–89%), followed by heart rate (73%, 72–75%), saturation (56%, 55–58%), and respiratory rate (51%, 50–53%), although the latter two had much wider ranges between countries. Figure 2a contains a heat map visualizing the frequency of vital sign measurements in participating countries. Variability between countries is apparent throughout all of the different vital signs and is most striking for respiratory rates. Temperature was the most consistent, as it was measured in more than 90% of cases in all countries but one.

Measurement of vital signs per triage level, age group and diagnosis

In the hospital in Turkey, no routine triage was performed. In the remaining hospitals, 99% (3825/3852) of children were triaged upon their arrival to the hospital. Children requiring 'very urgent' or 'immediate' care had their vital signs measured most frequently (Fig. 2b). Differences across triage levels were greatest for heart rate, saturation and respiratory rate and amounted to about 30%-points between the 'very urgent/immediate' and 'standard' categories (heart rate: 93% vs. 64%, saturation: 90% vs. 59%, respiratory rate: 65% vs. 37%).

Differences in measurement across age groups were smaller (Fig. 2c). Only heart rate and saturation were more frequently measured in infants than in children >5 years of age (heart rate: 83% vs. 71%; saturation 78% vs. 47%).

We observed an association between the measurement of vital signs and diagnosis (Fig. 2d). Most children (3307/4461, 74%) had respiratory tract infections (RTIs); only 15 children had sepsis or meningitis. Temperature and capillary refill were measured quite consistently across the different infectious foci (97% and 86% of cases respectively), but the remaining vital signs exhibited a considerable variability. Saturation was measured substantially more often in lower RTIs and in patients with sepsis/meningitis than in other cases. Heart rate was recorded in all patients with sepsis/meningitis (15/15) and in 86% (416/486) of those with lower RTIs. For fevers of unknown origin, on the other hand, heart rate measurements were included in the work-up of only 61% (174/284) of cases. Respiratory rates were measured in less than half of patients for four out of seven infectious foci and were done most frequently in patients with lower RTIs, amounting to 64% (310/486) of cases.

Fig. 2 Heat maps indicating the frequency of vital sign measurements in % (a) per country; (b) per triage level; (c) per age group; (d) per diagnosis.

a

	n hospitals	n (%)	Temperature	Capillary refill	Heart rate	Saturation	Respiratory rate	*Legend*
Italy	3	446 (10)						*0%*
Portugal	3	698 (15)						*10%*
Spain	4	631 (14)						*20%*
Romania	2	282 (6)						*30%*
Turkey	1	708 (16)						*40%*
Switzerland	2	428 (9)						*50%*
The Netherlands	5	161 (4)						*60%*
France	5	926 (20)						*70%*
Hungary	1	111 (2)						*80%*
Denmark	1	24 (0.5)						*90%*
England	1	145 (3)						*100%*
Total population		**4560 (100)**	**97**	**86**	**73**	**56**	**51**	

b

	n (%)	Temperature	Capillary refill	Heart rate	Saturation	Respiratory rate	*Legend*
Non-urgent	743 (19)						*30%*
Standard	1845 (48)						*40%*
Urgent	1042 (27)						*50%*
Immediate / Very urgent	195 (5)						*60%*
							70%
							80%
							90%
Total population[a]	**3825 (100)**	**97**	**83**	**69**	**66**	**43**	*100%*

c

	n (%)	Temperature	Capillary refill	Heart rate	Saturation	Respiratory rate	*Legend*
5 - 16 years	1054 (23)						*40%*
1 - 5 years	2478 (54)						*50%*
3 - 12 months	867 (19)						*60%*
0 - 3 months	160 (4)						*70%*
							80%
							90%
Total population[b]	**4559 (100)**	**97**	**86**	**73**	**56**	**51**	*100%*

d

	n (%)	Temperature	Capillary refill	Heart rate	Saturation	Respiratory rate	*Legend*
Fever without focus	284 (6)						*30%*
Other	199 (4)						*40%*
Urinary tract	125 (3)						*50%*
Enteric	531 (12)						*60%*
Upper respiratory	2821 (63)						*70%*
Lower respiratory	486 (11)						*80%*
Sepsis/meningitis	15 (0.3)						*90%*
							100%
Total population[c]	**4461 (100)**	**97**	**86**	**74**	**57**	**52**	

Footnote:

Superscript lowercase letters indicate the following: [a] Turkey (n=708) and 27 other cases excluded for missing triage level; [b] 1 patient missing age; [c] 99 (2%) missing diagnosis. Categories (country, diagnosis and triage level) are ranked from top to bottom according to how often all of the vital signs were measured. Vital signs are in turn organized from left to right based on their frequency of measurement overall. Green indicates highest frequency of measurement per figure; red indicates lowest frequency of measurement.

Frequency of abnormal findings

The incidence of abnormal vital signs when measured was generally low. Of all patients with a measured temperature, 2403 (54.2%) had a fever at the time of evaluation in the ED (Table 1). Out of these children, 889 (37%) had a temperature of 39 °C or more. Other than that, heart rate was most often abnormal, in 34.1% of cases. Twenty-nine percent of children were found to be tachypnoeic, hypoxia was found in 3.3% of cases and prolonged capillary refill in 1.5%.

We observed no correlation between the frequency of measurement of a vital sign per country and the proportion of abnormal values (out of all values measured in that country). So, less frequent measurement of a vital sign was not related to a higher proportion of abnormal values detected.

Adherence to guideline recommendation

From all hospitals using the NICE recommendations 1450/3014 (48%) of children under five underwent a complete measurement of these vital signs (95% CI 46 to 50%). A complete measurement was most frequent in children with lower RTIs and sepsis, although at a moderate compliance of 55% and 46% respectively (193/350 for lower RTIs and 5/11 for sepsis; Table 3). Multivariable analysis showed that children with RTIs had complete measurements significantly more often than children with fever without focus (odds ratio for upper RTI 1.75 (1.10–2.77), for lower RTI 3.75 (2.21–6.37); Table 3). Also, younger children

were more likely to have all recommended vital signs measured than children over one year of age. Last, children with high triage urgency had full measurements slightly more often than non-urgent children (immediate/very urgent OR 1.62 (0.95–2.76), urgent level OR 1.36 (0.96–1.95)). Crowding of the ED had no significant effect on the frequency of complete measurement of vital signs. After adjusting for diagnosis, age and triage urgency, a substantial variability between hospitals remained (data not shown).

Table 3. Determinants of full measurement of NICE-recommended vital signs in children under five.

Full chart measured	n/N (%)[a]	OR (95% CI)[b]
Diagnosis		
- Fever without focus	72/170 (42%)	Reference
- Other	53/134 (40%)	0.94 (0.50-1.77)
- Urinary tract infection	37/83 (45%)	1.19 (0.56-2.54)
- Enteric	142/352 (40%)	1.26 (0.75-2.12)
- Upper RTI	922/1856 (50%)	1.75 (1.10-2.77)
- Lower RTI	193/350 (55%)	3.75 (2.21-6.37)
- Sepsis-meningitis	5/11 (46%)	1.93 (0.49-7.65)
Triage level		
- Non-urgent	180/526 (34%)	Reference
- Standard	368/1117 (33%)	0.75 (0.54-1.05)
- Urgent	358/715 (50%)	1.36 (0.96-1.95)
- Immediate or very urgent	98/163 (60%)	1.62 (0.95-2.76)
Crowding of PED		
- Usual number of daily visits	519/1267 (41%)	Reference
- Less visits than usual	168/463 (36%)	0.83 (0.62-1.10)
- More visits than usual	296/775 (38%)	0.98 (0.77-1.24)
Age groups		
- 0 to 3 months	81/139 (58%)	1.76 (1.06-2.92)
- 3 to 12 months	392/728 (54%)	1.38 (1.09-1.75)
- 1 to 5 years	976/2146 (46%)	Reference

[a] based on population under five from hospitals using NICE recommendations, n = 3014

[b] multivariable analysis, clustered by hospital, based on complete cases, n = 2433;

RTI = respiratory tract infection; PED = paediatric emergency department

DISCUSSION

Main findings

In this study of febrile children at 28 European EDs, we observed that of all vital signs, temperature is most frequently measured and respiratory rate least frequently, but with a high degree of variability between countries. Most centres have adopted the recommendation of the NICE guideline *'Fever in under 5s: assessment and initial management'* to always measure temperature, heart rate, respiratory rate and capillary refill, but compliance to this recommendation was moderate. Febrile children that are under 1 year of age, with high triage urgency and those with RTIs were more likely to have a full set of vital signs measured.

Interpretation and comparison to existing literature

Fever was an inclusion criteria for our study, which explains the high frequency of completed temperature in our database and the high proportion of abnormal temperatures. The relatively high proportion with abnormal heart rate can be explained by the physiological relationship between temperature and heart rate.[22,23] Respiratory rate was least frequently measured and with large variation across subgroups. Other studies have suggested reasons for such variability, like crying or distress of a child, or limitations in the counting technique.[11,24,25] We had no information on the child's well-being or the devices used for measurement of respiratory rate, but these factors may have contributed to the observed low frequency of measurement of this vital sign. Although ED crowding has been associated with decreased quality of care [26], we found no association between ED crowding and adherence to the vital signs measurement recommendation in our study.

We observed an overall adherence of 48% to the NICE recommendation to measure four vital signs in all children under five, in our study in 2014-2016. This is lower than reported by a previous audit study in primary care in the UK (62%) after educational sessions and introduction of a template to record vital signs in the electronic health record.[15] An audit among paediatric EDs in the UK found that temperature was similarly measured as in our study (94%), but reports lower numbers for capillary refill time (53%) and higher rates for heart rate (94%) and respiratory rate (89%) measurements.[16] It may be striking that full measurement of vital signs children under five was most frequently done in children suspected of RTIs, rather than in those with suspected urinary tract infections and fever without focus. Even though the discharge diagnosis is often unknown at the moment of vital sign measurement, it is likely to assume that children with these last two diagnoses might present without specific symptoms. These children may have more diagnostic uncertainty and be at higher risk of complicated disease. Less than half of the children with suspected

sepsis – although represented by a small number in our study – received the full set of vital sign measurements needed for compliance with the NICE guidelines.

Patient characteristics can only partly explain the observed practice variations. Professional adherence to guideline recommendations can also be influenced by local policy or professional experience. Even though most participating centres mentioned that their guidelines were based on the NICE guideline, in the process of translation from the UK to another setting, the evidence probably is weighed according to the local setting and practice. This may induce further practice variation across centres.[18]

Strengths & limitations

This study had the advantage of a sizeable, prospectively generated database containing large amounts of high quality patient information from 28 hospitals of various sizes and hospital types, from 11 different countries in Europe. Compared to the available literature in European paediatric emergency medicine, this number of included hospitals and countries is large, supporting the generalizability of our findings. However, some countries and hospitals included more patients than others, which might have influenced results. Furthermore, countries were represented by different numbers of hospitals (some countries only by one hospital), which adds uncertainty to whether measurements are a reflection of national or local policies.

The study was performed in hospitals of the REPEM research collaboration, ensuring high quality data.[27] Their interest in research indicates that they are likely to uphold a high standard of care. The staff of participating hospitals were only aware of the general study design as a registry of febrile children, so a special focus on vital sign measurement during the study period is unlikely. Lastly, because this research treated missing variables as decisions not to perform certain measurements, some room remains for human error in data collection. However, all items in the data collection form were mandatory, with the option to fill in 'missing'. During the preparation of this manuscript the local investigators confirmed that 'missing' values were indeed 'not recorded'.

Clinical and research implications

Our numbers on compliance to the NICE recommendation obtained from 28 European EDs calls for better recording of vital signs in children. Not measuring vital signs may pose children at risk of underestimating the severity of their illness or delaying necessary treatments.[14] Even though almost all included centres had adopted the NICE recommendation to measure vital signs in all febrile children, compliance in less than half of cases is striking. Even in children

with sepsis, fever without source or urinary tract infections in less than 50% of cases the full set was measured. Therefore, special attention should be given to children presenting with fever without specific symptoms, since vital sign measurements may contribute most to the identification of severe infections in this patient group. Although measurement is influenced by age and triage, it might be questioned whether triage appropriately selects children with severe disease.[28]

Future research should focus on identifying reasons for non-compliance, including cultural and healthcare factors at the individual, organizational and national level.[18] Qualitative research could provide more in-depth information on the reasons for the observed discrepancies in vital sign measurements across Europe. At the same time, more evidence is needed on the diagnostic value of vital signs in different settings and patient groups and their impact on health outcomes. Such research could provide evidence for targeted measuring of vital signs in children that benefit most from complete measurements.

Conclusion

Measuring vital signs in children with fever in the emergency department occurs with a high degree of practice variation between different European hospitals and is done more often in younger children, those with a higher triage urgency or who have respiratory tract infections. The overall adherence to the NICE recommendation to measure four vital signs in all febrile children under five is moderate. Our practice variation study is essential as a benchmark for current clinical practice. It can guide future research into the drivers and consequences of the observed under-recording of vital signs. Moreover, it can be used to tailor implementation strategies of the NICE recommendation to different European settings.

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Chapter 2.2.

The influence of chest X-ray results on antibiotic prescription for childhood pneumonia in the emergency department

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Submitted

ABSTRACT

The aim of this study is to evaluate the influence of chest X-ray (CXR) results on antibiotic prescription in children suspected of lower respiratory tract infections (RTI) in the emergency department (ED). We performed a secondary analysis of a stepped-wedge, cluster randomized trial of children aged 1 month to 5 years with fever and cough/dyspnoea in 8 EDs in the Netherlands (2016-2018), including a 1-week follow-up. We analysed the observational data of the pre-intervention period, using multivariable logistic regression to evaluate the influence of CXR result on antibiotic prescription. We included 597 children (median age 17 months [IQR 9-30, 61% male). CXR was performed in 109/597 (18%) of children (range across hospitals 9% to 50%); 52/109 (48%) showed focal infiltrates. Children who underwent CXR were more likely to receive antibiotics, also when adjusted for clinical signs and symptoms, hospital and CXR result (OR 7.25 [95% CI 2.48-21.2]). Abnormalities on CXR were not significantly associated with antibiotic prescription.

Conclusion: Performance of CXR was independently associated with more antibiotic prescription, regardless of its results. The limited influence of CXR results on antibiotic prescription highlights the inferior role of CXR on treatment decisions for suspected lower RTI in the ED.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the leading causes of childhood morbidity and mortality worldwide. Although in Western countries mortality has significantly declined, CAP continues to cause a high burden of disease.[1] Pneumonia is a common reason for children to visit the emergency department (ED) and contributes to substantial use of medical services, including hospitalization, emergency care visits and antibiotic use.[2,3]

Chest radiography (CXR) was long considered the reference standard for diagnosing CAP in children with suspected lower respiratory tract infections (RTI). However, more recent evidence shows the limitations of CXR in guiding the management of these children, like the high inter-observer variability, inability to distinguish viral from bacterial pneumonia and radiation exposure.[4-7] In 2011, guidelines for the management of childhood CAP were published in Europe and the United States,[5,6] recommending against routine use of CXR in most children in the outpatient setting, and restricting the use of CXR to children with moderate to severe signs and symptoms of CAP at risk of developing complications.

Some studies have evaluated the impact of the CAP guidelines on diagnosis and treatment of childhood CAP, and did not find significant changes in CXR performance rates.[8-11] However, their study populations were limited to children with a confirmed diagnosis of CAP rather than those with signs and symptoms of a lower RTI, and they did not evaluate the impact of CXR results on antibiotic treatment. Little is known on how the CXR is currently used in antibiotic treatment decisions in the broad population of children with signs and symptoms of a lower RTI in the paediatric ED.

This study is a secondary analysis of a stepped-wedge, cluster randomized trial, that evaluated the impact of a clinical decision rule on antibiotic prescription in children under five years of age with a suspected lower RTI in the ED (STRAP trial).[12] In the current study, we used the pre-intervention (usual care) data of this trial to evaluate the influence of CXR results on antibiotic prescription in children with suspected lower RTI in the ED.

METHODS

Study design

We used usual care data from the Study to Reduce Antibiotic prescription in childhood Pneumonia (STRAP, Netherlands Trial Register, NTR5326).[12] STRAP is a stepped-wedge cluster randomized trial, implementing a validated clinical prediction model (the Feverkidstool)[13] in the EDs of eight hospitals in The Netherlands. In this secondary analysis, we only used data from the pre-intervention period, when usual care was provided. During usual care the patients were first triaged and assessed by a nurse. Then they were evaluated by a physician, who decided on additional diagnostics and treatment. Usual care was provided according to the Dutch guideline for febrile children,[14] which is in line with the international CAP guidelines of the British Thoracic Society and the Infectious Diseases Society of America, including the recommendation to not routinely perform a CXR in the outpatient setting.[5,6] Detailed methods of the trial have been published earlier.[12]

Population

We included children aged one month to five years presenting to the ED with fever (≥38.5° Celsius or reported by parents) and symptoms of a lower RTI (cough, dyspnea or tachypnea) from January 1, 2016 to March 11, 2018. Exclusion criteria were comorbidities (immunodeficiency, multiple handicaps, congenital heart defects, chronic pulmonary disease, or preterm birth <32 weeks and aged <1 year old at the time of ED visit), use of antibiotics in the week prior to inclusion, amoxicillin allergy, another identifiable infectious focus other than lower respiratory (e.g. cutaneous, otitis, tonsillitis), signs of complicated lower RTI at presentation (saturation <85%, respiratory insufficiency, empyema, sepsis).

Outcomes

The outcome measure for this study was antibiotic prescription (yes/no) at the end of the ED visit.

Data collection and definitions

Data were obtained using a standardized case record form completed during the ED visit and during telephone follow-up 7 days after the ED visit. We collected data on patient's general characteristics, clinical signs and symptoms, diagnostic tests, discharge diagnosis, treatment and strategy failure. Discharge diagnosis was determined by the treating physician at the time of ED evaluation. We used the following predefined definition of strategy failure that was used in the trial: secondary hospitalization or secondary or switched antibiotic prescription during follow-up, oxygen need or fever at day 7 or the development of complications (parapneumonic effusion, pleura-empyema, lung abscess, respiratory insufficiency).

The CXR results were defined based on the routine report of the radiologist in the electronic patient record. CXR results were classified as focal infiltrate if the report included "infiltrate", "consolidation" or "pneumonia". Reports including "atelectasis", "diffuse abnormality" and "perihilar abnormality" were classified as diffuse or perihilar abnormalities. If "pleural effusion" or "empyema" were reported, the CXR was classified as "pleural effusion". If the CXR report included the terms "normal chest", "no abnormalities" or "clear lungs", this was considered a normal CXR result.[15]

Statistical analyses

We used logistic regression to test the influence of the performance and results of a CXR on antibiotic prescription, adjusted for clinical signs and symptoms and hospital variability. We could include 17 predictors in our multivariable model. Next to 'hospital' and 'CXR result', we included the following clinical predictors in the model: age, sex, ill appearance, hypoxia (oxygen saturation <94%), tachypnea, retractions (as a marker of increased work of breathing) and C-reactive protein (CRP) level, that are known predictors for bacterial pneumonia, based on the literature and guidelines.[5,6,13] Missing predictor variables were imputed 10 times using the mice package in R (version 3.3.2).[16] The imputation model included relevant information about clinical signs and symptoms, diagnostic work up and outcome, treatment, and follow-up. Analyses were performed on all 10 databases and the results were pooled. We used IBM SPSS Statistics version 24 and R (version 4.0.0) for data management and analyses.

Ethics

The Erasmus MC Medical Ethics Committee granted ethical approval for the STRAP study (MEC-2014-332) and written informed consent was obtained from all participants.

RESULTS

Baseline characteristics

We included a total of 597 children, with a median age 17 months (IQR 9–30) and 364/597 (61%) were male (Table 1). Ill appearance was present in 220/572 (38%), hypoxia in 144/595 (24%) of children, and median CRP level was 19 mg/L (7–44). Antibiotics were prescribed in 179/597 (30%) of the children and 329/597 (55%) of the children were hospitalized. The majority of children improved within a week after ED visit, but strategy failure was observed in 131/597 (22%), most frequently due to secondary antibiotic prescription or fever at day 7.

Chest X-ray use

In 109/597 (18%) of the population a CXR was performed. This varied across hospitals from 11/123 (9%, 95%CI 4–14%) to 10/20 (50%, 95%CI 28-72%). Of the 109 obtained CXRs, 52 (48%) showed focal infiltrates, 31 (28%) showed diffuse or perihilar findings and 26 (24%) showed no abnormalities. None of the CXRs showed pleural effusion.

Table 1. Baseline characteristics

General characteristics	n (%)
Hospital	
Hospital A	69/597 (12%)
Hospital B	35/597 (6%)
Hospital C	144/597 (24%)
Hospital D	123/597 (21%)
Hospital E	82/597 (14%)
Hospital F	95/597 (16%)
Hospital G	29/597 (5%)
Hospital H	20/597 (3%)
Triage level	
Immediate	13/506 (3%)
Very urgent	293/506 (58%)
Urgent	146/506 (29%)
Standard or non-urgent	54/506 (11%)
Clinical characteristics	
Male sex	364/597 (61%)
Age in years, median (IQR)	17 (9-30)
Duration of fever in days, median (IQR)	2 (1-4)
Ill appearance	220/572 (38%)
Cough	555/581 (96%)
Dyspnea	432/581 (74%)
Oxygen saturation <94%	144/595 (24%)
Diagnostic work-up	
C-reactive protein test done	375/597 (63%)
C-reactive protein, median (IQR)	19 (7-44)
Chest X-ray result	
Normal	26/597 (4%)
Focal infiltrate/consolidation	52/597 (9%)
Diffuse/perihilar abnormality	31/597 (5%)

Table 1. (continued)

Discharge diagnosis	
Pneumonia	204/594 (34%)
Bronchiolitis	117/594 (20%)
Upper RTI	176/594 (30%)
Viral induced wheeze	69/594 (12%)
Subglottic laryngitis	21/594 (4%)
Other	7/594 (1%)
Therapy and follow-up	
Antibiotic prescription	179/597 (30%)
Hospitalization	329/597 (55%)
Strategy failure	131/597 (22%)
Strategy failure, reasons:	0/597 (0%)
Secondary antibiotic prescription	45/597 (8%)
Changed antibiotic prescription during follow-up[a]	14/597 (2%)
Secondary hospitalization	16/597 (3%)
Oxygen need at day 7	9/597 (2%)
Fever at day 7	47/597 (8%)

Footnote: [a]including one ICU-admission

Influence of chest X-ray performance and result on antibiotic prescription

Figure 1 shows the flow of children from ED presentation to 7 days after the ED, including the performance and results of the CXR, antibiotic prescription and strategy failure. Of the 52 children with a focal infiltrate on the CXR, all but nine received antibiotics. Four of these nine untreated children had strategy failure during follow-up (all had secondary antibiotic prescription). Strategy failure was higher in children who underwent a CXR (34/108, 31%) than in those who did not (97/464, 21%). More than half (32/57, 56%) of the children with diffuse/perihilar or no abnormalities on their CXR received antibiotic treatment. Of all children that underwent CXR, 69% (75/109) received antibiotics, versus 21% (104/488) of children that did not undergo CXR.

When we adjusted for hospital variability, clinical signs and symptoms and result of the CXR in a multivariable analysis, we found that the mere performance of a CXR was independently associated with antibiotic prescription (OR 7.25 [95% CI 2.48-21.2]), see Table 2. Older age, CRP-level and ill appearance were other predictors for antibiotic prescription. Abnormalities on CXR (focal or diffuse/perihilar abnormalities) showed higher odds ratios (Table 2), but were not significantly associated with antibiotic prescription.

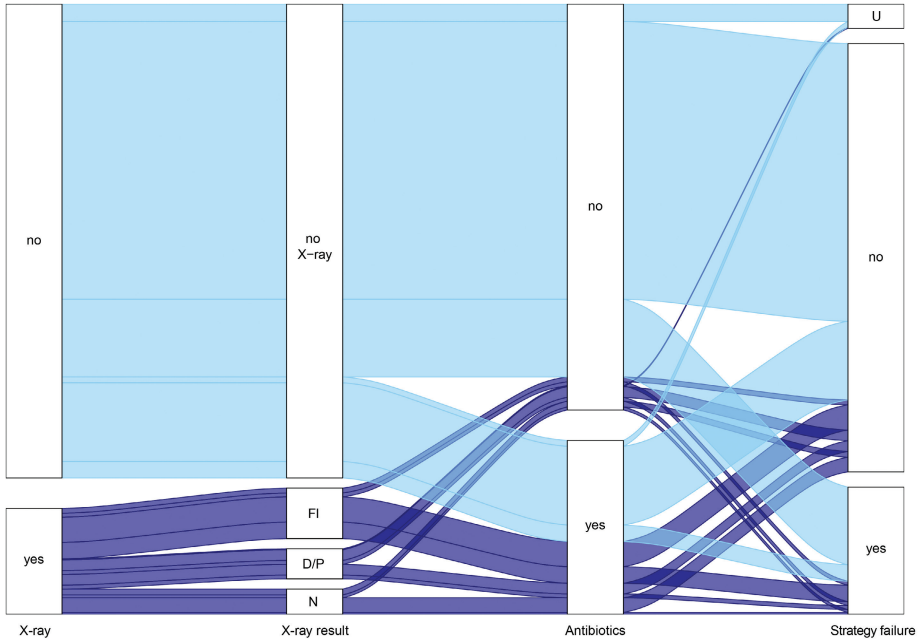

Figure 1. Flow of patients from ED visit to follow-up

Footnotes: Light blue = no chest X-ray; dark blue = chest X-ray performed. FI = focal infiltrate; D/P = diffuse/perihilar findings; N = normal; U = unknown.

Table 2. Influence of CXR performance and result on antibiotic prescription

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hospital		
Hospital H	reference	reference
Hospital A	0.76 (0.21-2.7)	0.89 (0.16-5.12)
Hospital B	1.19 (0.31-4.57)	0.58 (0.08-4.01)
Hospital C	1.54 (0.48-4.88)	2.92 (0.65-13.19)
Hospital D	1.47 (0.46-4.71)	2.29 (0.49-10.81)
Hospital E	2.31 (0.71-7.54)	2.14 (0.43-10.68)
Hospital F	3.19 (0.99-10.23)	2.92 (0.6-14.12)
Hospital G	2.44 (0.65-9.22)	5.59 (0.99-31.63)
Age (months)	**1.04 (1.02-1.05)**	**1.02 (1.01-1.04)**
Gender (female)	1.09 (0.77-1.56)	1.12 (0.67-1.85)
Ill appearance	**4.14 (2.84-6.04)**	**2.68 (1.54-4.68)**
Tachypnea	**1.83 (1.07-3.11)**	1.31 (0.61-2.82)
Hypoxia (<94%)	1.33 (0.89-1.98)	0.77 (0.43-1.4)
Retractions	1.14 (0.78-1.66)	1.26 (0.72-2.23)

Table 2. (continued)

CRP (mg/L)	**1.04 (1.03-1.05)**	**1.04 (1.03-1.05)**
Chest X-ray performed (yes)	**8.09 (5.11-12.8)**	**7.25 (2.48-21.2)**
Chest X-ray result		
Normal	reference	reference
Focal infiltrate	2.53 (0.86-7.46)	1.88 (0.48-7.32)
Diffuse / perihilar abnormalities	0.5 (0.17-1.45)	0.32 (0.08-1.29)

DISCUSSION

Main results

In a multicentre population of children under five years presenting with a suspected lower RTI in eight paediatric EDs, a CXR was performed in 18%. Almost half of these CXRs showed focal infiltrates and a quarter showed diffuse or perihilar findings. The decision to perform a CXR as part of the diagnostic work-up was associated with more frequent antibiotic prescription. This association remained after correcting for hospital variation, clinical signs and symptoms and result of the CXR. Results of the CXR, as presence of focal or diffuse abnormalities, were not significantly associated with antibiotic prescription.

Interpretation and comparison with previous studies

The high number of abnormalities on performed CXRs in our population suggests that physicians ordering them already had a high clinical suspicion of CAP and that their clinical judgements were generally accurate. We observed variability in CXR use across hospitals, which has been reported previously, although not always at individual patient level.[8,17,18] The observed variability in CXR use across participating hospitals in our study is similar to previous findings from studies with similar inclusion criteria based on respiratory symptoms, showing CXR performance rates between 9% and 36%.[17,19,20]

It is striking that the decision to perform a CXR was independently associated with antibiotic treatment but the results of the CXR were not. Nearly half of children with normal CXRs still received antibiotics. Similar to our results, previous studies have shown that a CXR does not result in changes in management,[4,7] and that antibiotic prescription decisions depend on the physician's intention to treat, regardless of the CXR result.[21] Previous studies have also shown that children who undergo CXR are more likely to receive antibiotics, despite low numbers of diagnosed pneumonia.[19,22] Other factors, like clinical assessment, appear to be more important than CXR results in the decision to prescribe antibiotics.

The current guidelines recommend to not routinely perform a CXR in case of non-complicated CAP.[5,6] The children in our population mostly had uncomplicated disease at presentation, given the fact that none of the CXRs showed pleural effusion or empyema. Strategy failure was present in 22% of children, but it must be noted that this was using a broad trial definition,[12] including signs of a prolonged disease course like fever at day 7. So, in our non-complex population (without comorbidities or prior antibiotic treatment), the chances of detecting a complicated pneumonia on CXR are very low, confirming the guideline recommendations.

Strengths and limitations

To the best of our knowledge, this is the first European study that evaluated CXR use in children with suspected CAP in the ED after the publication of the international guidelines for the management of childhood CAP (British and US guidelines published in 2011, Dutch guideline in 2013).[5,6,14] Strengths of our study include its prospective and multicentre design and well-defined, broad study population. We included children with signs and symptoms of lower RTIs rather than children diagnosed with CAP, reflecting more accurately the population of children presenting to the ED.

The results of this study should be interpreted in the light of the following limitations. First, the population is limited to a trial population. Even though we used the pre-intervention data only, the use of the trial's strict exclusion criteria may have affected the generalizability of our results to the complete ED population. Second, we adjusted for clinical signs and symptoms in our regression model, but we did not have information on the exact considerations of the physicians to order a CXR or not. Last, we did not consider the inter-observer variability between radiologists and paediatricians in our analyses. For our analysis we intentionally used the radiologist's reading exclusively, because this was most consistently available. We collected data on the radiologist's as well as the paediatrician's CXR readings and found a kappa of 0.59 for agreement (i.e. moderate agreement), which is similar to previous studies.[23-25] The high inter-observer variability is a well-recognized limitation of CXR.[26]

Implications

Our results show there is a very limited role of the CXR in the diagnostic and therapeutic pathway of childhood CAP in ED settings. In line with the current guidelines, performance of a CXR in non-complex children suspected of a lower RTI should be discouraged. In the absence of a gold standard for CAP, we need other tools to support the physician's decisions on diagnostics and treatment. Clinical decision rules based on individual risk prediction of bacterial infections may be used for this purpose.[12,13,27,28] Other upcoming diagnostic

techniques for diagnosing childhood CAP are point of care lung ultrasound and new point of care biomarkers.[29] Further improvement of these new techniques is necessary to support the physician's decisions.

Conclusion

CXR is still frequently performed in non-complex children suspected of lower RTIs. CXR use was associated with more antibiotic prescriptions, regardless of the CXR results. The limited influence of CXR results on antibiotic prescription highlights the inferior role of CXR in treatment decisions. Our findings support the guideline recommendations against routine use of CXR for children with uncomplicated CAP. Further research should aim to identify new diagnostic techniques in order to optimize the management of childhood pneumonia.

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Chapter 2.3

Antibiotic prescription for febrile children in European emergency departments: a cross-sectional, observational study

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SUMMARY

Background Prevalence of serious bacterial infections in children in countries in western Europe and the USA is low. Antibiotic stewardship aims at a more rational use of antibiotics but information on the frequency of antibiotic prescription to children in emergency departments is scarce. We aimed to quantify and explain variability in antibiotic prescription in children attending European paediatric emergency departments.

Methods We did a cross-sectional, observational study of children aged between 1 month and 16 years who presented with fever to one of 28 European emergency departments on one random sampling day per month between Nov 1, 2014, and Feb 28, 2016. The surveyed sites were spread across 11 countries and included 17 academic hospitals with 3000 to up to 80 000 annual visits to their paediatric emergency departments. We determined the proportion of children without comorbidities who received antibiotic prescriptions by country, focus of infection, and type of antibiotic. We then did a detailed analysis of the same population, using a multilevel logistic regression analysis, into the variability in prescriptions across hospitals, focusing particularly on respiratory tract infections and correcting for a combination of result-dependent factors. Random group assignment was done by computer randomisation.

Findings Of 5177 children in total, 617 children had comorbidities. Of the 4560 children without comorbidities, 1454 (32%) received antibiotics. This percentage varied from 19% to 64% across countries. Of these 1454 prescriptions issued, 893 (61%) were second-line antibiotics. Antibiotic prescription for respiratory tract infections, the most common infection type, in children without comorbidities was most variable across countries (15–67% for upper respiratory tract infections and 24–87% for lower respiratory tract infections) and was associated with age (odds ratio [OR] 1.51, 95% CI 1.08–2.13), fever duration (OR 1.45, 1.01–2.07), blood concentrations of C-reactive protein (OR 2.31, 1.67–3.19), and chest x-ray results (OR 10.62, 5.65–19.94, for focal abnormalities; OR 3.49, 1.59–7.64, for diffuse abnormalities). After correcting for patient characteristics, diagnostic assessment, and hospital characteristics, antibiotic prescription for respiratory tract infections remained highly variable across emergency departments (standardised antibiotic prescription ratio 0.49–2.04).

Interpretation Antibiotic prescription in European emergency departments is highly variable, with frequent use of second-line antibiotics. To ensure successful antibiotic stewardship initiatives in Europe aimed at reducing unnecessary prescription of antibiotics, variability of prescription across hospitals should be considered, drivers of suboptimal antibiotic prescription at the local level need to be identified, and European guidelines need to be devised.

INTRODUCTION

Fever is one of the most frequent reasons for children to visit the emergency department.[1] A small proportion (5–15%) of these children have a serious bacterial infection, of which respiratory tract infections cause the highest mortality.[2] Variability in the management of respiratory tract infections suggests that there is overdiagnosis of bacterial infections and overtreatment with antibiotics,[3-5] fuelling antibiotic resistance.[6] To reduce inappropriate antibiotic use, antibiotic stewardship programmes have been launched worldwide[7] but few of them include the emergency department.[8] Studies on antibiotic prescription in febrile children often focus on primary care or in-hospital settings.[9,10] Information about antibiotic prescription in emergency department settings is mostly derived secondarily from studies of selected populations, and it is not supported by primary studies.[11] To implement effective interventions for antibiotic stewardship, having access to data from emergency departments on antibiotic prescription and understanding the factors that influence antibiotic prescription in this setting is then crucial. This cross-sectional, observational study aims to fill this gap by answering the following questions: (1) what is the current proportion of antibiotic prescriptions given to febrile children visiting European paediatric emergency departments; and (2) can differences in patient characteristics, diagnostic assessment, or hospital setting explain the variability in antibiotic prescription?

METHODS

Study design and participants

We did a cross-sectional, observational study at European paediatric emergency departments (figure 1). 28 hospitals participating in the Research in European Pediatric Emergency Medicine (REPEM) network were invited.[12] We included children aged between 1 month and 16 years who visited the emergency department with fever as the reason for consultation, irrespective of additional symptoms, between Nov 1, 2014, and Feb 28, 2016. We excluded patients if they repeatedly visited the emergency department for the same problem within 7 days, if they had used antibiotics 7 days before their visit to the emergency department, and if they had an antibiotic allergy. This study was approved by the medical ethics committee of the Erasmus Medical Center (MEC-2014–419) and local feasibility was approved by the ethics committees of all participating hospitals. The need for obtaining written informed consent was waived, except by the ethics committee of Cruces Hospital, Bilbao, Spain. These local researchers obtained written informed consent from all their participants. The protocol development and conduct of the study was done without collaboration with patient groups.

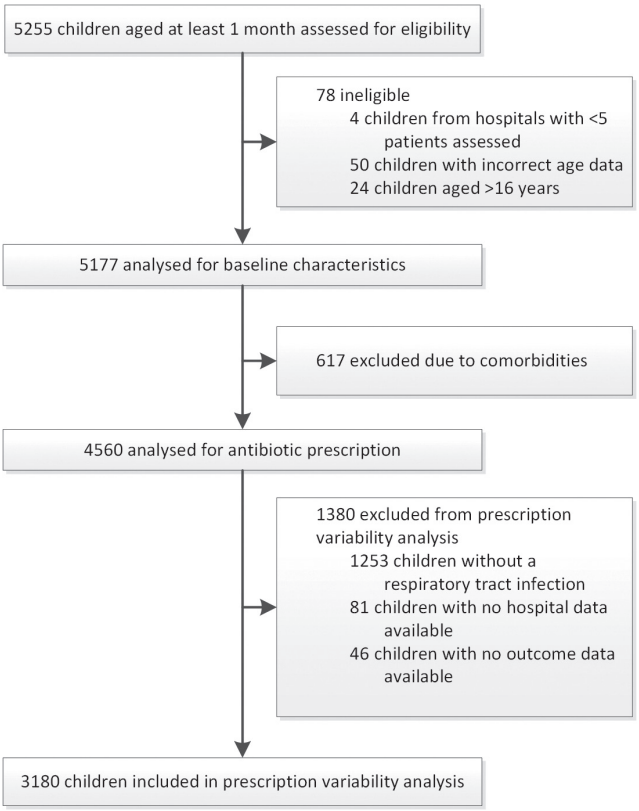

Figure 1: Study profile

Procedures

Each month, hospitals were randomly assigned one sampling day. Hospitals were divided into ten groups, and each group was randomly assigned to one calendar day each month via computer randomisation. All hospitals participated in data collection for 12 consecutive months. A sampling day ran from 0730 h to 0730 h (24 h) and there was a period of 2–6 weeks between sampling days. To avoid inclusion bias, we collected data from all children who met our inclusion criteria and visited the emergency department on the random sampling days. Data were prospectively collected via an electronic questionnaire (appendix) that included general characteristics of the patient, method of referral, triage level, clinical signs and symptoms, additional diagnostics (table 1), presumed focus of infection at time of discharge from the emergency department, treatment, and disposition. All questionnaire items were mandatory but always included the option "not known". Each hospital had one or two physicians dedicated to data collection. 1 week before each sampling day, the responsible physician for each hospital was informed of the date, and a reminder email with instructions for data collection was sent by the principal investigator on the sampling

day. After a sampling day, data integrity was evaluated by the principal investigator and the local physicians who collected the data were provided with feedback on completeness and potential errors, in order to optimise the data collection process. Information on immunisation coverage for 2014–16 was retrieved from the WHO UNICEF Review of National Immunization Coverage 1980–2017 database. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report this study.

Outcome measures

Our primary analysis was the proportion of children who received an antibiotic prescription on discharge from the emergency department. We grouped the prescribed antibiotics into first-line and second-line antibiotics. The first-line antibiotics were amoxicillin, narrow-spectrum penicillins (benzylpenicillin and flucloxacillin), first-generation cephalosporins, and erythromycin. The second-line antibiotics were doxycycline, broad-spectrum penicillins (ampicillin, coamoxiclav, and piperacillin plus tazobactam, excluding amoxicillin), second-generation and third-generation cephalosporins (cefuroxime, cefotaxime, and ceftriaxone), sulfonamide plus trimethoprim, macrolides excluding erythromycin, aminoglycosides, fluoroquinolones, vancomycin, and metronidazole.[13]

Statistical analysis

In the descriptive analyses, we compared children with and without comorbidities. Relevant comorbidities were defined as cardiovascular, respiratory, renal, haematological or immunological, neuromuscular, genetic defects, malignancy, and multiple comorbidities. When information about comorbidities was missing, we assumed that no relevant comorbidity was present. In addition, we evaluated the proportion of children who were prescribed antibiotics by country and by focus of infection in children without comorbidities. In these and further analyses, children with comorbidities were excluded because of an increased risk for serious infections or a more serious disease course. We used a multilevel logistic regression model (clustered by hospital) to calculate the influence of patient-level determinants, diagnostic assessment, and specific hospital determinants on antibiotic prescription for respiratory tract infections in more detail. For this analysis, we excluded children with another focus of infection, children with missing data on the outcome of antibiotic prescription, and children from hospitals with missing information on hospital determinants. The null model included an intercept only. Model 1 included patient-level risk factors for serious bacterial infections, based on clinical prediction rules and guidelines[14-16] from the UK National Institute for Health and Care Excellence: age, sex, fever duration, ill appearance, temperature, tachycardia, tachypnoea, oxygen saturation, capillary refill time, decreased consciousness, work of breathing, petechiae, meningeal signs, focus of

infection, referral method, and the season of the emergency department visit. In model 2, diagnostic assessment was added to the analysis, which included the performance and results of C-reactive protein tests and chest x-rays. We tested the linearity of the associations of continuous predictors with the main outcome of antibiotic prescription using splines. Potentially meaningful interactions were included in the model if they improved the model fit. For the final model, we considered hospital characteristics that have been suggested in previous publications to influence antibiotic prescription,[17-19] namely: national health-care system, hospital type (academic, teaching, or non-teaching), crowding (number of emergency department visits on sampling days), specialist responsible in the emergency department, first doctor evaluating the child, mode of supervision, availability of guidelines for respiratory tract infections, and vaccine coverage. We considered paediatric health-care systems (where >75% of children are under the primary care of a paediatrician), general practice systems (general practitioners offer primary care to >75% of children), or combined systems.[19] Supervision could be direct (supervising specialist is physically present at the emergency department), indirect (supervising specialist is not at the emergency department but can be reached by phone and come to the emergency department if needed within 20–30 min), or a combination of direct and indirect supervision.[20] We selected hospital variables for our final model on the basis of the validity of the data, the plausibility of the predictor influencing antibiotic prescription, and the added value of the predictor in our model. We calculated the standardised antibiotic prescription ratio (between observed and expected number of antibiotic prescriptions in a hospital) on the basis of the null model (crude prescription) and the final model (adjusted prescription), illustrated by a bar plot. A number of 1 indicates the average prescribing hospital based on the model, a number above 1 indicates excess prescriptions, and a number below 1 means fewer prescriptions than expected on the basis of the model predictions. For regression analysis, missing data were imputed ten times using the mice package in R (version 3.3.2). An imputation model was used to draw plausible data values from a distribution specifically designed for each missing data point, including all available variables, general information, clinical signs and symptoms, diagnostics, treatment, and disposition. Analyses were done on all ten datasets and results were pooled.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors approved the final version of the manuscript submitted for publication.

RESULTS

A total of 5177 children from 28 emergency departments in 11 countries were included in the analysis of baseline characteristics (figure 1, table 1, appendix). Their median age was 2.5 years (IQR 1.1–4.9) and 2838 (55%) were male. 256 (5%) children were triaged as needing immediate or very urgent care and most children were self-referred. 17 hospitals were academic and the other 11 were teaching or non-teaching hospitals. 17 hospitals were in city centres and the rest were regional or mixed (serving a region incorporating both rural and urban areas) hospitals. The capacities of the hospitals ranged from fewer than 5000 paediatric annual emergency department visits (six hospitals) to more than 25 000 (12 hospitals). In most hospitals, a paediatrician-in-training was the first doctor to evaluate febrile children, supervised by a fully trained paediatrician or a paediatric emergency physician. 1757 (34%) children underwent additional diagnostics, most often urinalysis. The most common focus of infection was the upper respiratory tract (3105 [60%] children; figure 2), and only 19 (<1%) children had sepsis or meningitis. The presumed cause of infection was most often reported as viral (3278 [63%] children). Children with comorbidities (617 [12%]) were generally older and more ill than those without comorbidities, as evidenced by their higher triage levels and higher number of abnormal signs and symptoms. These children were subjected to more diagnostic tests and were more frequently admitted for hospital treatment or monitoring but received antibiotics just as often as children without comorbidities (1454 [32%] of 4560 children without comorbidities received prescriptions vs 206 [33%] children with comorbidities; table 1).

Table 1: Baseline characteristics of the enrolled population

	Without comorbidity (n = 4560)		With comorbidity (n = 617)	
	Proportion of patients (n[%])*	Patients with missing data (n[%])	Proportion of patients (n[%])*	Patients with missing data (n[%])
General characteristics				
Male sex†	2451 (54%)	3 (<1%)	387 (63%)	
Median age (years)†	2.4 (1.1-4.7)	1 (<1%)	3.2 (1.5-5.9)	
Season†				
Spring	1110 (24%)		127 (21%)	
Summer	766 (17%)		86 (14%)	
Autumn	1024 (23%)		160 (26%)	
Winter	1660 (36%)		244 (40%)	
Way of referral†		36 (1%)		10 (2%)
General practitioner	395 (9%)		57 (9%)	
Self	3966 (87%)		509 (83%)	

Table 1: (continued)

	Without comorbidity (n = 4560)		With comorbidity (n = 617)	
	Proportion of patients (n[%])*	Patients with missing data (n[%])	Proportion of patients (n[%])*	Patients with missing data (n[%])
Other	163 (4%)		41 (7%)	
Triage level†		710 (16%)		34 (6%)
Immediate or very urgent	197 (4%)		59 (10%)	
Urgent	1042 (23%)		246 (40%)	
Standard	1866 (41%)		192 (31%)	
Non-urgent	745 (16%)		86 (14%)	
Signs and symptoms				
Ill appearance†	431 (10%)	60 (1%)	88 (14%)	14 (2%)
Median duration of fever in days (IQR)	1 (0.5-2.1)	58 (1%)	1 (0.5-2)	13 (2%)
Mean temperature in °C (SD)	38 (1)	125 (3%)	38.1 (1)	18 (3%)
Mean oxygen saturation in %† (SD)	98 (2.5)	1993 (44%)	97 (3.4)	165 (27%)
Tachycardia†	1138 (25%)	1219 (27%)	185 (30%)	147 (24%)
Tachypnoea†	665 (15%)	2227 (49%)	128 (21%)	301 (49%)
Increased work of breathing†	352 (7%)	40 (1%)	128 (21%)	7 (1%)
Prolonged capillary refill time	67 (2%)	650 (14%)	11 (2%)	100 (16%)
Decreased level of consciousness†	23 (1%)	17 (<1%)	13 (2%)	4 (1%)
Petechiae present†	41 (1%)	62 (1%)	11 (2%)	9 (1%)
Meningeal signs present	10 (<1%)	84 (2%)	3 (<1%)	8 (1%)
Additional diagnostics				
Median concentration of blood C-reactive protein in mg/L (IQR)	16.2 (5.4-51.8)	3820 (84%)	25.3 (5.4-51.8)	457 (74%)
Leukocyte count x10^9/L	11.8 (7.8-16.3)	3855 (85%)	12 (1-16.7)	469 (76%)
Median concentration of procalcitonin in ng/mL (IQR)	0.21 (0.10-0.78)	4422 (97%)	0.26 (0.14-0.20)	582 (94%)
Blood culture†	224 (5%)		56 (9%)	
Urinalysis†	841 (18%)		140 (23%)	
X-ray done†	431 (10%)		131 (21%)	
Lumbar puncture done	34 (1%)		7 (1%)	
Treatment				
Antibiotic prescription	1454 (32%)	61 (1%)	206 (33%)	7 (1%)
Disposition†		6 (<1%)		1 (<1%)
Discharged	4035 (88%)		471 (76%)	
Observation unit <24 h	187 (4%)		48 (8%)	
Admitted to ward	321 (7%)		90 (15%)	
Admitted to intensive care unit	11 (<1%)		6 (1%)	

*Comorbidities are cardiovascular, respiratory, renal, haematological or immunological, neuromuscular, genetic defects, malignancy, or multiple comorbidities. *Unless stated otherwise. †Significantly different between children with and without comorbidities (p<0.05).*

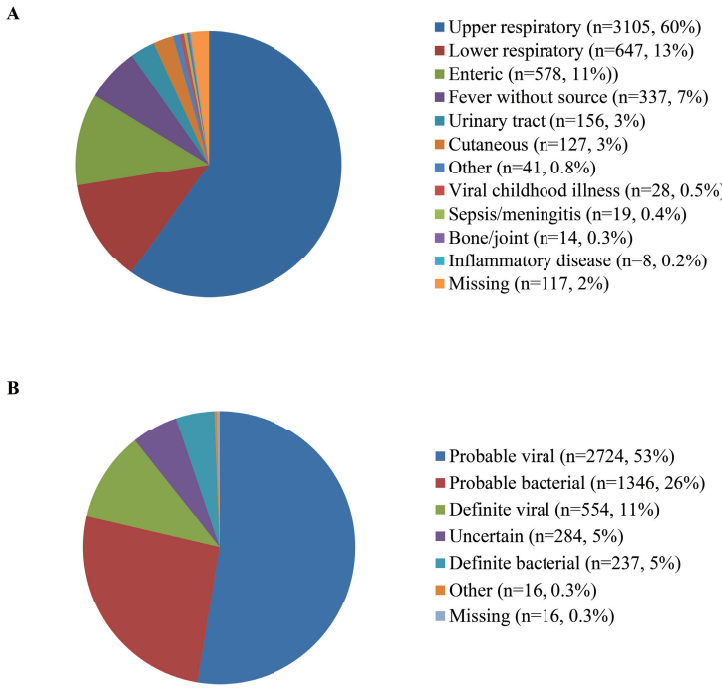

Figure 2. Frequency of probable focus (A) and cause (B) of infection in all 5177 children studied.
For full data, see appendix.

893 (61%) of the prescriptions issued to children without comorbidities were second-line antibiotics (table 2, appendix). The overall proportion of antibiotic prescriptions ranged from 19% to 64% across countries. Overall, countries with high antibiotic prescriptions also prescribed second-line antibiotics more often. We then analysed the proportion of children without comorbidities who received a prescription by focus of infection (figure 3). The five most common foci of infection were identified in 4247 (93%) of these children. 22 (4%) of 531 children with enteric infections received antibiotics, with low variability between countries. Children with urinary tract infections were prescribed antibiotics most frequently (116 [93%] of 125). Children with respiratory tract infections, comprising 73% (n=3307) of the evaluated patients without comorbidities, accounted for 83% (1208 of 1454) of all antibiotic prescriptions. The mean proportion of prescriptions for lower respiratory tract infections was higher than that for upper respiratory tract infections (227 [47%] of 486 vs 981 [35%] of 2821 children respectively), with high variability in prescription between countries for both. Antibiotics were prescribed for 37% of respiratory tract infections in children without comorbidities (n=1208). Variation in prescriptions for upper respiratory tract infections was 15–67% across hospitals, and 24–87% for lower respiratory tract infections.

Table 2. Antibiotic prescriptions per country in children without comorbidities

	Proportion of children prescribed antibiotics	Proportion of prescription for second-line antibiotics	Children with missing data
Total population	1454/4560 (32%)	893/1454 (61%)	61/4560 (1%)
Per country			
Turkey	450/708 (64%)	363/450 (81%)	46/708 (6%)
UK	57/145 (39%)	45/57 (79%)	1/145 (1%)
Hungary	41/111 (37%)	29/41 (71%)	4/111 (4%)
Italy	149/446 (33%)	120/149 (81%)	6/446 (1%)
Romania	87/282 (31%)	81/87 (93%)	2/282 (1%)
Spain	161/631 (26%)	68/161 (42%)	
Portugal	177/698 (25%)	56/177 (32%)	2/698 (<1%)
Denmark	6/24 (25%)	2/6 (33%)	
Netherlands	37/161 (23%)	18/37 (49%)	
France	208/926 (22%)	70/208 (34%)	
Switzerland	81/428 (19%)	41/81 (51%)	

Countries are ordered from high to low percentage of antibiotic prescriptions. Second-line antibiotics are represented as percentage out of the total number of antibiotic prescriptions per country.

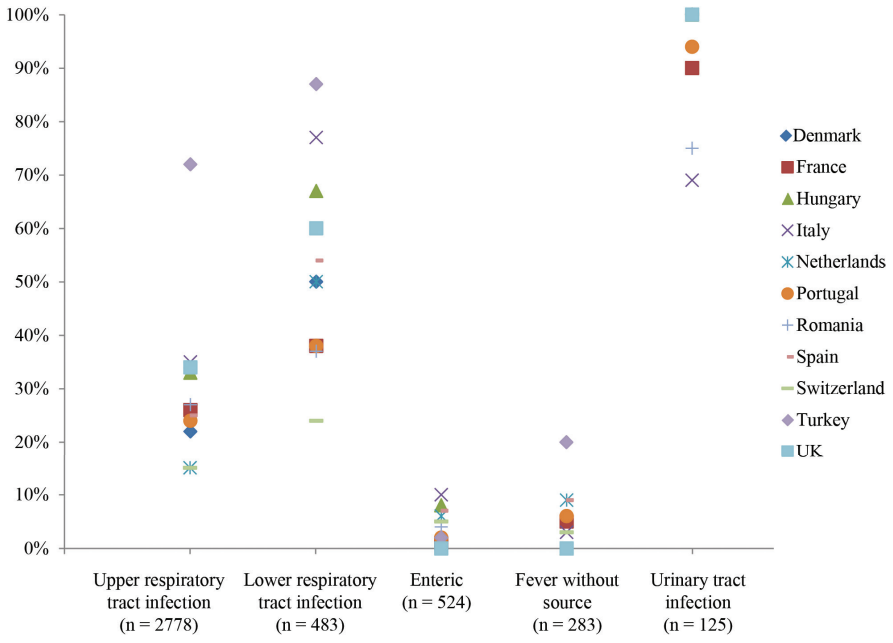

Figure 3: Variability in antibiotic prescription across countries for the most frequent foci of infection in 4560 children without comorbidities.
For full data, see appendix.

We based our multilevel analysis on children with respiratory tract infections from the 26 of 28 hospitals (n=3180) for which information on hospital determinants was available. Figure 4A presents the crude number of antibiotic prescriptions (standardised prescription) based on the null model. An increased standardised prescription ratio indicates that more antibiotics are prescribed than expected and a decreased standardised prescription ratio indicates that fewer antibiotics are prescribed than expected, based on the average prescribing hospital. In the intermediate models (appendix), we added patient characteristics, diagnostic assessment, and hospital characteristics, leading to the final model (table 3). Older age and longer duration of fever were associated with an increased likelihood of antibiotic prescription. Other significant predictors were high blood concentrations of C-reactive protein and focal or diffuse abnormalities in the chest x-ray. At hospital level, we were limited to two variables: hospital type and national health-care system. Even though these factors did not significantly influence antibiotic prescription individually, they yielded the best model fit. All factors included in the analysis could only explain part of the variability in antibiotic prescription between hospitals. After adjustment for all factors in the model, the rank of hospitals according to proportion of prescriptions issued changed and the variability in prescription by hospital was slightly decreased (figure 4B). However, substantial variability in prescription remained, ranging from half to twice the number of prescriptions as the average prescribing hospital in our dataset. Even though specific determinants of antibiotic prescription could be identified in the whole population of patients, differences in patient mix, diagnostic assessment, or hospital characteristics could not explain all variability in antibiotic prescription.

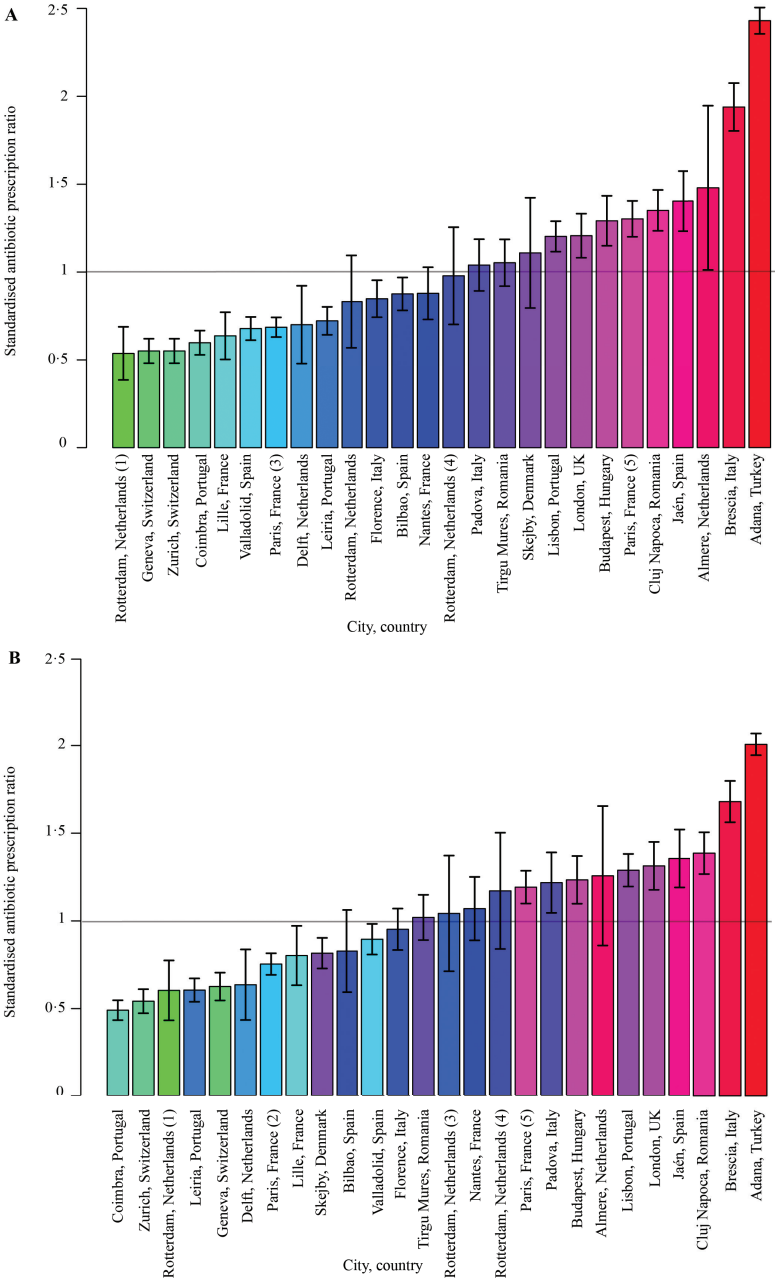

Figure 4: Standardised antibiotic prescription for respiratory tract infections per hospital

(A) Null model (crude standardised antibiotic prescription). (B) Final model (adjusted standardised antibiotic prescription for patient characteristics, diagnostic assessment, and hospital characteristics). Hospital determinants for Hôpital Antoine Béclère (Paris, France) and Hospital de Mendaro (Mendaro, Spain) were not available, so they were not included in this analysis. 1 Erasmus Medical Center Sophia Children's Hospital. 2 Hôpital Robert Debré. 3 Maasstad Ziekenhuis. 4 Sint Franciscus Ziekenhuis. 5 Hôpital Necker–Enfants Malades.

Table 3. Final multilevel model for antibiotic prescription in children with respiratory tract infections

Final model	Odds Ratio (95% CI)
Intercept	0.66 (0.16-2.84)
Patient characteristics	
Age (years)*	**1.51 (1.08-2.13)***
Age (years)* ‡	0.65 (0.35-1.21)
Female sex	0.88 (0.73-1.07)
Season (spring=reference)	
Summer	0.81 (0.59-1.11)
Autumn	1.13 (0.84-1.53)
Winter	0.87 (0.65-1.15)
Way of referral (general practice= reference)	
Self-referral	1.25 (0.82-1.92)
Other	0.76 (0.39-1.46)
Triage level (very urgent=reference)	
Urgent	0.9 (0.5-1.63)
Standard	0.69 (0.38-1.24)
Non-urgent	0.65 (0.34-1.25)
Ill appearance	0.97 (0.66-1.44)
Duration of fever (days)*	**1.45 (1.01-2.07)***
Duration of fever (days)* ‡	0.6 (0.27-1.33)
Temperature (°C)*	1.43 (0.99-2.08)
Temperature (°C)* ‡	0.69 (0.24-1.94)
Temperature (°C)* §	1.27 (0.02-83.24)
Oxygen saturation (%)*	0.96 (0.86-1.07)
Tachycardia	1.09 (0.85-1.39)
Tachypnoea	0.9 (0.69-1.18)
Increased work of breathing	0.69 (0.43-1.09)
Prolonged capillary refill (>3s)	1.26 (0.58-2.73)
Decreased level of consciousness	0.3 (0.07-1.34)
Petechiae	1.96 (0.72-5.33)
Meningeal signs	1.75 (0.06-54.57)
Focus (lower RTI *vs* upper RTI)	1.19 (0.8-1.76)
Diagnostic assessment	
C-reactive protein tested	1.04 (0.71-1.54)
C-reactive protein concentration (mg/l)*	**2.31 (1.67-3.19)***
X-ray result (not done =reference)	
Normal	0.68 (0.42-1.11)
Focal abnormalities	**10.62 (5.65-19.94)***
Diffuse abnormalities	**3.49 (1.59-7.64)***
Hospital	
Hospital type (teaching *vs* academic)	1 (0.49-2.04)
Health-care system (paediatric system=reference)	
Combined system	1.28 (0.46-3.6)
General practice system	1.21 (0.4-3.64)

*Tachycardia and tachypnoea were defined according to the Advanced Paediatric Life Support guidelines.[21] RTI=respiratory tract infection. *Standardised value. †Significant predictor. ‡Second coefficient (non-linear term: spline with 3 or 4 degrees of freedom). §Third coefficient (non-linear term: spline with 3 or 4 degrees of freedom).*

DISCUSSION

Our study provides insights into the prescription of antibiotics to febrile children on the basis of a prospective registry across a wide range of European emergency departments. Our results indicate that antibiotic prescription varies substantially between countries and hospitals and that second-line antibiotics are frequently used. We also identified that respiratory tract infections are the most common type of infection with highest variability in antibiotic prescription between paediatric emergency departments. The variability of antibiotic prescription for respiratory tract infections cannot be fully explained by differences in patient characteristics, diagnostic assessment, and measured hospital characteristics. The main strength of our study is that it provides a prospective European registry of antibiotic prescription collected in a standardised way in 11 countries, enabling comparisons across a large part of Europe. Hospitals were invited through the REPEM network, which ensured broad European participation and high-quality data. The selected hospitals have an interest in research collaboration and might therefore be more homogeneous in the type of care they provide or have a higher standard of care than hospitals that were not included. The number of included hospitals per country does not match the country's population size.[22] Even though we included very diverse hospitals in terms of type and size, the true antibiotic prescription in European emergency departments might be even higher and more variable than we observed. The size of the hospital largely matches the number of included patients per hospital, suggesting no major selection bias. Hospitals Erasmus Medical Center, Netherlands, and Cukurova, Turkey, sampled on more days immediately before or after the assigned sampling days. Since these extra days were still random, we assume this did not introduce selection bias in our study. A registry study might be susceptible to the Hawthorne effect but local physicians were only aware of the general scope of this study (registry of febrile children) and not particularly about the monitoring of antibiotic prescription. There are some limitations to this approach. First, four of 11 countries participated with only a single hospital, so we were not able to take clustering at country level into account. Second, some hospitals had small sample sizes (five hospitals included <50 patients), thereby limiting the power to show large differences between hospitals. Nevertheless, our results still showed substantial variability, so this limitation did not hamper our conclusions. Third, we did not include the risk of serious bacterial infection per country in our model because it is already related to clinical signs and symptoms that we did include. Finally, the large proportion of unexplained variability might indicate that there are other contributing factors that we did not include in our model. The statistical limitation of the number of hospital factors that we could include might be one cause of the large remaining unexplained variance. As we have corrected extensively for many known possibly influential factors, we still believe our analysis

lead to valid conclusions. Overall antibiotic prescription variation in our study is consistent with previous reports (27% and 55%),[17,23] in particular for upper respiratory tract infections.[24] Antibiotic prescription for respiratory tract infections and for lower respiratory tract infections is generally reported to be higher than we observed.[25] Studies on fever without a source usually focus on children below 3 months of age, whereas the minimum age of our population was 1 month, explaining why our observed antibiotic prescription was lower than in other studies.[16] Large variability in antibiotic prescription between European countries has been reported previously but did not focus on paediatric emergency care.[26] The fact that prescription variability was highest for children with respiratory tract infections in our study could have several reasons. First, respiratory tract infections might include multiple diagnoses, such as acute otitis media, bronchiolitis, or pneumonia, for which there are different specific guidelines and different likelihoods of bacterial or viral origin.[14,27] We had no information available on these specific diagnoses but since we collected data in each hospital throughout a full year, we believe all of these types of respiratory tract infections were represented in our data for all countries. The criteria for diagnoses could have varied between hospitals, hence a standardised diagnostic protocol for presumed focus of infection and confirmed diagnosis (where possible) might assist in future studies. Second, and probably most important, is the lack of a gold standard for the diagnosis of bacterial respiratory tract infections. When a decision on treatment is made, there is often diagnostic uncertainty and bacterial causes can often not be excluded, influencing diagnostic assessment and the likelihood of antibiotic prescription.[5] Although we found some specific drivers of antibiotic prescription, they could only explain a small proportion of the observed variability between hospitals. Similar results were obtained by a large US observational study, showing broad unexplained variability in antibiotic prescription for respiratory tract infections across primary paediatric practices.[3] The influence of patient characteristics (age and duration of fever) and diagnostic tests on antibiotic prescription we found was generally consistent with previously reported predictors of bacterial infections.[15,16] The effect of different infection foci (lower vs upper respiratory tract infection) was strongly correlated with the effect of the chest x-ray result. A notable finding was our observation that focal as well as diffuse abnormalities in the chest x-ray strongly increased the chance of antibiotic prescription, even though their low diagnostic value has been well described.[28] We did not include procalcitonin in our analyses, since this test was only done in isolated cases in less than half of the participating hospitals, reflecting the infrequent use of the biomarker test in routine practice during the study period. We were particularly interested to ascertain whether hospital characteristics affected antibiotic prescription and if they could explain variability. We were able to include two specific hospital factors in our model that define differences across local practices in the evaluation of febrile children: hospital type and national health-care system. These factors

added most to our model in terms of reducing variance and were assumed to be meaningful. By including health-care system and method of referral in our model, we aimed to cover aspects of the primary care system but we did not have detailed data on primary care in each country because this analysis was beyond the scope of our study. Other potential factors were excluded from the model. Emergency department crowding had a negligible effect on antibiotic prescription and our data were not very consistent for this parameter.[29] All hospitals had guidelines for the diagnosis and treatment of respiratory tract infections but we lacked information on the contents or implementation of these guidelines. There was low variability in immunisation coverage, so we assumed that this factor could not explain any substantial variance in antibiotic prescription. Coverage of vaccination against *Haemophilus influenzae* type B was more than 90% in all participating countries without variation, according to the WHO UNICEF Review of National Immunization Coverage 1980–2017 database. Pneumococcal conjugate vaccine coverage was above 75% in all countries with available data, a threshold that has been described as sufficient to uphold herd immunity.[30] Only Romania did not carry out pneumococcal conjugate vaccination at the time of data collection. Children were included throughout the entire 24 h of the sampling day—ie, also in evening and night shifts, both on weekdays and weekends. Choosing sampling days at random aimed to reduce systematic effects introduced by shift schedules, such as variable capacity of supervision. Our findings that antibiotic prescription for respiratory tract infections is dependent on the hospital and that second-line antibiotics are widely used are crucial for all clinicians, researchers, and policy makers who plan interventions to reduce unnecessary prescription of antibiotics, particularly second-line drugs. Our study was not designed to evaluate the validity of the decision to prescribe an antibiotic; however, the finding of large unexplained variability across hospitals does suggest overprescription. Given that most antibiotics are prescribed to children with respiratory tract infections but this occurs with high variability, strategies aiming to reduce antibiotic prescription could be most beneficial in this patient group. Particularly, overuse of second-line antibiotics should be addressed as a priority in such strategies. Successful national examples[25] should be extrapolated to a wider setting by international implementation studies and by developing European guidelines. The expected effect of an intervention can nevertheless vary per setting, since not all factors that affect antibiotic prescription have yet been explained and baseline prescription varies between emergency departments. This variation not only affects sample size calculations for different settings but also emphasises the need for multicentre studies on the outcomes of strategies aiming to reduce the inappropriate use of antibiotics. To ensure successful antibiotic stewardship initiatives at the European level, factors associated with suboptimal antibiotic prescription in individual hospitals and nationally need to be identified.

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SUPPLEMENTARY APPENDIX

Appendices available on the website of Lancet Infectious Diseases:

- Case Report Form (CRF) patient data
- Case Report Form hospital data

Baseline characteristics of the hospitals

Hospital	Country (code)	n	Annual PED visits	Type	Setting	Paediatric healthcare system	Responsible specialist	First doctor	Mode of supervision	Discussed with supervisor?	Hib coverage	PCV coverage
Aarhus Universitetshospital, Skejby	Denmark (DK)	32	5000	Academic	Mixed	GP system	Paediatrician	paediatrics resident / EM resident	Indirect/ combination	always	>90	>90
Hopital Antoine Béclère, Paris	France (FR)	58	25000	Academic	Inner city	Combined system	NA	NA	NA		>90	>90
Hôpital Mère-Enfant, Nantes		153	NA	Academic	Inner city		Paediatrician	paediatrics resident	Direct	always	>90	>90
Hôpital Necker-Enfants malades, Paris		333	66000	Academic	Inner city		PEM specialist	PEM specialist	Direct	often	>90	>90
Hopital Robert Debre, Paris		431	88000	Academic	Inner city		Paediatrician	paediatrics resident / EM resident / paediatrician / emergency physician	Direct	often	>90	>90
Roger Salengro Hospital, Lille		103	25000	Teaching	Inner city		PEM specialist	paediatrics resident	Direct	always	>90	>90
Heim Pal Children's Hospital, Budapest	Hungary (HU)	135	30000	Teaching	Mixed	Combined system	Paediatrician	paediatrician / paediatricss resident	Direct	often	>90	>90
Meyer University Children's Hospital, Florence	Italy (IT)	175	42000	Academic	Inner city	Combined system	Paediatrician	paediatricss resident / PEM specialist	Direct	always	>90	87-89
Ospedale dei Bambini, Azienda Ospedaliera Spedali Civili, Brescia		195	36500	Academic	Mixed		Paediatrician	paediatrician	Direct	always	>90	87-89
University Hospital, Padova		116	25000	Academic	Inner city		Paediatrician	paediatrics resident / paediatrician	Indirect/ combination	often	>90	87-89

Hospital	Country (code)	n	Annual PED visits	Type	Setting	Paediatric healthcare system	Responsible specialist	First doctor	Mode of supervision	Discussed with supervisor?	Hib coverage	PCV coverage
ErasmusMC – Sophia, Rotterdam	The Netherlands (NL)	99	4000	Academic	Inner city	GP system	Paediatrician	paediatrics resident	Indirect/ combination	always	>90	>90
Flevoziekenhuis, Almere		26	5000	Teaching	Mixed		Paediatrician	paediatrics resident	Indirect/ combination	always	>90	>90
Maasstad Ziekenhuis, Rotterdam		34	3500	Teaching	Inner city		Paediatrician	paediatrics resident	Indirect/ combination	always	>90	>90
Reinier de Graaf, Delft		40	2643	Teaching	Mixed		Paediatrician	paediatrics resident	Indirect/ combination	always	>90	>90
Sint Franciscus Ziekenhuis, Rotterdam		26	2700	Teaching	Inner city		Paediatrician	paediatrics resident	Indirect/ combination	always	>90	>90
Centro Hospitalar de Leiria, Leiria	Portugal (PT)	215	46000	Teaching	Mixed	Combined system	Paediatrician	paediatrics resident / paediatrician	Direct	often	>90	NA
Lisbon Medical Academic Center (Hospital de Santa Maria), Lisboa		353	50000	Academic	Inner city		Paediatrician	paediatrics resident	Direct	often	>90	NA
Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra		275	60000	Academic	Inner city		Paediatrician	paediatrics resident / paediatrician	Direct	often	>90	NA
Emergency Children's Hospital, Cluj Napoca	Romania (RO)	179	9400	Teaching	Regional	GP system	Paediatrician or PEM	paediatrics resident / EM resident	Direct	always	>90	NA
Tirgu Mures Emergency Clinical County Hospital, Tirgu Mures		122	16000	Academic	Inner city		Paediatrician	paediatrics residemt / EM resident / PEM specialist	Direct	always	>90	NA

Hospital	Country (code)	n	Annual PED visits	Type	Setting	Paediatric healthcare system	Responsible specialist	First doctor	Mode of supervision	Discussed with supervisor?	Hib coverage	PCV coverage
Cruces University Hospital Bilbao, Basque country	Spain (ES)	277	53000	Academic	Inner city	Paediatric system	PEM specialist	paediatrics resident / emergency physician	Indirect/ combination	always	>90	NA
Hospital de Mendaro, Mendaro (Guipúzcua)		71	7160	Non-teaching	Regional		NA	NA	NA		>90	NA
Hospital Universitario Rio Hortega, Valladolid		266	24000	Teaching	Mixed		PEM specialist	paediatrics resident	Indirect/ combination	often	>90	NA
San Agustín University Hospital, Linares, Jaén		106	NA	Teaching	Mixed		Paediatrician	emergency physician	Indirect/ combination	often	>90	NA
University Hospital, Geneva	Switzerland (CH)	265	25500	Academic	Inner city	Combined system	PEM specialist	paediatrics resident	Direct	often	>90	80-81
Children's Hospital of Zurich, Zurich		205	37000	Academic	Inner city		Emergency physician	emergency physician	Direct	often	>90	80-81
Cukurova University Medical Faculty Balcali Hospital, Adana	Turkey (TK)	740	20000	Academic	Mixed	Combined system	PEM specialist	paediatrician	Direct	always	>90	>90
St Mary's Hospital, London	United Kingdom (UK)	147	27000	Academic	Inner city	GP system	PEM specialist	paediatrics resident / PEM resident	Indirect/ combination	always	>90	>90

GP = general practitioner; PEM = paediatric emergency medicine; NA = not available; Hib = Haemophilus Influenzae type b; PCV = Pneumococcal Conjugate Vaccine
n: less than 50 patients included / 50 – 150 / >150. Annual PED visits: <5000 annual paediatric ED visits / 5000 – 25000 / >25000

Baseline characteristics per country

	Total population		**Denmark (DK)**		**France (FR)**		**Hungary (HU)**		**Italy (IT)**		**The Netherlands (NL)**	
	n = 5177		**n = 32**		**n = 1078**		**n = 135**		**n = 486**		**n = 225**	
General characteristics	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*
Male gender	2838 (54.8)	3 (<0.1)	10 (31.3)		602 (55.8)	2 (0.2)	81 (60)	1 (0.7)	256 (52.7)		117 (52)	
Age in years, median (IQR)	2.5 (1.1-4.9)	1 (<0.1)	1.9 (0.7 - 4.3)		1.9 (0.9 - 4)		2.1 (1 - 4.9)		2.4 (1.2 - 4.5)		2.3 (1 - 4.2)	
Comorbidity	617 (11.9)		8 (25)		152 (14.1)		24 (17.8)		40 (8.2)		64 (28.4)	
Way of referral		46 (0.9)		1 (3.1)		7 (0.6)				8 (1.6)		16 (7.1)
- *General practitioner*	452 (8.7)		23 (71.9)		104 (9.6)		19 (14.1)		15 (3.1)		115 (51.1)	
- *Self*	4475 (86.4)		3 (9.4)		938 (87)		109 (80.7)		442 (90.9)		48 (21.3)	
- *Other*	204 (3.9)		5 (15.6)		29 (2.7)		7 (5.2)		21 (4.3)		46 (20.4)	
Triage level		744 (14.4)				12 (1.1)		2 (1.5)				14 (6.2)
- *Immediate or very urgent*	256 (4.9)		0 (0)		33 (3.1)		17 (12.6)		3 (0.6)		73 (32.4)	
- *Urgent*	1288 (24.9)		3 (9.4)		244 (22.6)		56 (41.5)		73 (15)		93 (41.3)	
- *Standard*	2058 (39.8)		15 (46.9)		509 (47.2)		58 (43)		332 (68.3)		43 (19.1)	
- *Non-urgent*	831 (16.1)		14 (43.8)		280 (26)		2 (1.5)		78 (16)		2 (0.9)	
Treatment												
Antibiotic prescription	1660 (32.1)	68 (1.3)	9 (28.1)		260 (24.1)		47 (34.8)	6 (4.4)	162 (33.3)	10 (2.1)	56 (24.9)	
Hospitalization	663 (12.8)	8 (0.2)	13 (40.6)		124 (11.5)	1 (0.1)	61 (45.2)		75 (15.4)		80 (35.6)	1 (0.4)

	Total population n = 5177		Portugal (PT) n = 843		Romania (RO) n = 301		Spain (ES) n = 720		Switzerland (CH) n = 470		Turkey (TR) n = 740		United Kingdom (UK) n = 147	
General characteristics	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*	*n (%) or median (IQR)*	*missing*
Male gender	2838 (54.8)	3 (<0.1)	453 (53.7)		162 (53.8)		382 (53.1)		263 (56)		418 (56.5)		94 (63.9)	
Age in years, median (IQR)	2.5 (1.1-4.9)	1 (<0.1)	3.3 (1.4 - 5.8)		2.9 (1.2 - 5.5)		2.1 (1 - 4.5)		2 (0.9 - 4.4)		3.2 (1.4 - 6.2)		2.6 (1.3 - 4.7)	
Comorbidity	617 (11.9)		145 (17.2)		19 (6.3)		89 (12.4)		42 (8.9)		32 (4.3)		2 (1.4)	
Way of referral		46 (0.9)				1 (0.3)		2 (0.3)				5 (0.7)		6 (4.1)
- *General practitioner*	452 (8.7)		48 (5.7)		6 (2)		45 (6.3)		54 (11.5)		10 (1.4)		13 (8.8)	
- *Self*	4475 (86.4)		781 (92.6)		251 (83.4)		662 (91.9)		404 (86)		725 (98)		112 (76.2)	
- *Other*	204 (3.9)		14 (1.7)		43 (14.3)		11 (1.5)		12 (2.6)		0 (0)		16 (10.9)	
Triage level		744 (14.4)		1 (0.1)				1 (0.1)				712 (96.2)		2 (1.4)
- *Immediate or very urgent*	256 (4.9)		23 (2.7)		11 (3.7)		17 (2.4)		53 (11.3)		3 (0.4)		23 (15.6)	
- *Urgent*	1288 (24.9)		229 (27.2)		221 (73.4)		184 (25.6)		128 (27.2)				57 (38.8)	
- *Standard*	2058 (39.8)		276 (32.7)		36 (12)		463 (64.3)		248 (52.8)		23 (3.1)		55 (37.4)	
- *Non-urgent*	831 (16.1)		314 (37.2)		33 (11)		55 (7.6)		41 (8.7)		2 (0.3)		10 (6.8)	
Treatment														
Antibiotic prescription	1660 (32.1)	68 (1.3)	216 (25.6)	2 (0.2)	97 (32.2)	2 (0.7)	191 (26.5)		93 (19.8)		471 (63.6)	47 (6.4)	58 (39.5)	1 (0.1)
Hospitalization	663 (12.8)	8 (0.2)	34 (4)		79 (26.2)	3 (1)	69 (9.6)		82 (17.4)	1 (0.2)	29 (3.9)	2 (0.3)	17 (11.6)	

Antibiotic prescription

Antibiotic prescription	N = 4560	n (%)	missing, n (%)
Overall antibiotic prescription		1454 (31.9)	61 (1.3)
Details of antibiotic prescription	**N = 1454**		
Broad spectrum antibiotics		893 (61.4)	36 (2.5)
Class of antibiotics			36 (2.5)
-- *Penicillines*		1089 (74.9)	
-- *Other betalactam antibiotics*		171 (11.8)	
-- *Macrolides*		100 (6.9)	
-- *Other antibiotics*		14 (1)	
-- *Combination of classes*		44 (3)	
Route of administration			23 (1.6)
-- *oral*		1193 (82)	
-- *intravenous*		120 (8.3)	
-- *intramuscular*		118 (8.1)	

Frequency of probable focus and cause of infection (data for figure 2)

Probable focus of infection	
Upper respiratory	3105 (60%)
Lower respiratory	647 (13%)
Enteric	578 (11%)
Fever without source	337 (7%)
Urinary tract	156 (3%)
Cutaneous	127 (3%)
Other	41 (0.8%)
Viral childhood illness	28 (0.5%)
Sepsis/meningitis	19 (0.4%)
Bone/joint	14 (0.3%)
Inflammatory disease	8 (0.2%)
Missing	117 (2%)
Total	**5177**
Probable cause of infection	
Probable viral	2724 (53%)
Probable bacterial	1346 (26%)
Definite viral	554 (11%)
Uncertain	284 (5%)
Definite bacterial	237 (5%)
Other	16 (0.3%)
Missing	16 (0.3%)
Total	**5177**

Variability in antibiotic prescription across countries for the 5 most common foci of infection in children without comorbidities (data for figure 3)

	Population n	Upper RTI	Lower RTI	Enteric	Fever without source	Urinary tract
Focus n		*2821*	*486*	*531*	*284*	*125*
Turkey	708	393/584 (67%)	27/31 (87%)	1/45 (2%)	1/5 (20%)	25/25 (100%)
United Kingdom	145	31/93 (33%)	6/10 (60%)	0/7 (0%)	0/4 (0%)	4/4 (100%)
Hungary	111	23/70 (33%)	10/15 (67%)	1/14 (7%)	0/2 (0%)	6/6 (100%)
Italy	446	91/259 (35%)	36/48 (75%)	7/70 (10%)	1/35 (3%)	9/13 (69%)
Romania	282	68/182 (37%)	11/32 (34%)	2/51 (4%)	0/3 (0%)	6/8 (75%)
Spain	631	97/387 (25%)	31/58 (53%)	4/55 (7%)	7/79 (9%)	16/16 (100%)
Portugal	698	103/435 (24%)	37/98 (38%)	1/67 (1%)	1/16 (6%)	17/18 (94%)
Denmark	24	2/9 (22%)	3/6 (50%)	0	0/5 (0%)	1/1 (100%)
France	926	126/487 (26%)	41/109 (38%)	2/144 (1%)	5/95 (5%)	17/19 (89%)
The Netherlands	161	10/68 (15%)	12/24 (50%)	2/35 (6%)	1/11 (9%)	4/4 (100%)
Switzerland	428	37/247 (15%)	13/55 (24%)	2/43 (5%)	1/29 (3%)	11/11 (100%)
Total	4560	981/2821 (35%)	227/486 (47%)	22/531 (4%)	17/284 (6%)	116/125 (93%)

Total n top 5 foci of infection	4247/4560 (93%)
Total n RTIs	3307/4560 (73%)
Total proportion antibiotics prescribed	1454/4560 (32%)
Antibiotics prescribed for RTIs out of all antibiotics	1208/1454 (83%)

Chapter 3.

Supporting treatment decisions for childhood pneumonia

Chapter 3.1.

Can clinical prediction models assess antibiotic need in childhood pneumonia? A validation study in paediatric emergency care

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ABSTRACT

Objectives

Pneumonia is the most common bacterial infection in children at the emergency department (ED). Clinical prediction models for childhood pneumonia have been developed (using chest x-ray as their reference standard), but without implementation in clinical practice. Given current insights in the diagnostic limitations of chest x-ray, this study aims to validate these prediction models for a clinical diagnosis of pneumonia, and to explore their potential to guide decisions on antibiotic treatment at the ED.

Methods

We systematically identified clinical prediction models for childhood pneumonia and assessed their quality. We evaluated the validity of these models in two populations, using a clinical reference standard (1. definite/probable bacterial, 2. bacterial syndrome, 3. unknown bacterial/viral, 4. viral syndrome, 5. definite/probable viral), measuring performance by the ordinal c-statistic (ORC). Validation populations included prospectively collected data of children aged 1 month to 5 years attending the ED of Rotterdam (2012-2013) or Coventry (2005-2006) with fever and cough or dyspnoea.

Results

We identified eight prediction models and could evaluate the validity of seven, with original good performance. In the Dutch population 22/248 (9%) had a bacterial infection, in Coventry 53/301 (17%), antibiotic prescription was 21% and 35% respectively. Three models predicted a higher risk in children with bacterial infections than in those with viral disease (ORC $\geq$0.55) and could identify children at low risk of bacterial infection.

Conclusions

Three clinical prediction models for childhood pneumonia could discriminate fairly well between a clinical reference standard of bacterial versus viral infection. However, they all require the measurement of biomarkers, raising questions on the exact target population when implementing these models in clinical practice. Moreover, choosing optimal thresholds to guide antibiotic prescription is challenging and requires careful consideration of potential harms and benefits.

INTRODUCTION

Community-acquired pneumonia is the second largest cause of childhood mortality worldwide.[1] Despite improvements over the past decades, lower respiratory tract infections are still responsible for 103.3 deaths per 100,000 people in children under five years globally, with large differences across regions.[2] Respiratory tract infections are also a common reason for emergency department (ED) visit and the most frequent indication for antibiotic prescription in children.[1,3] Discriminating bacterial infections that require antibiotic treatment from viral, self-limiting disease is one of the biggest diagnostic challenges in childhood pneumonia. Chest x-ray is no longer recommended as the gold standard for bacterial pneumonia,[4] and routinely available biomarkers are not pathognomonic for this diagnosis.[5] At the same time, accurate diagnosis of bacterial infection is crucial, since misuse of antibiotics is associated with increased antimicrobial resistance, which in turn also causes morbidity and mortality.[6] Current antibiotic prescription for suspected pneumonia in Western countries ranges from 23-59% with wide acknowledgement that a considerable proportion of these antibiotics are not necessary.[3,7]

In order to standardize the evaluation and treatment of children suspected of pneumonia, clinical decision support systems could be useful tools to classify children into a high or low risk profile.[8] Multiple clinical prediction models for childhood pneumonia have been developed. Even though their current use in clinical practice is limited, they may play a role as treatment decision support, thereby improving rational antibiotic prescription. However, since those models are mainly developed with chest x-ray as their reference standard, it is unclear if they can also validly predict a clinically based diagnosis of pneumonia. Moreover, the question is whether these models can be translated into clinical practice by guiding decisions on antibiotic treatment.

This study aims to systematically search available clinical prediction models for childhood pneumonia in ED settings in high-income countries, to evaluate their validity using a new, clinical diagnosis reference standard, and to explore their potential to guide decisions on antibiotic treatment.

METHODS

Selection and quality assessment of prediction models

A systematic search for prediction models of childhood pneumonia was performed in Embase, Medline Ovid, Web of science, PubMed and Google scholar in September 2017. We included studies on diagnosis and treatment of uncomplicated childhood pneumonia in ED settings in Western countries published since 2000 (see search strategy and exclusion criteria, S1 Text). JvdM and BK performed the selection independently, discrepancies were discussed within the research group and decided using consensus.

We evaluated the clinical prediction models for their quality and diagnostic value. Quality assessment was performed by JvdM and checked by RO, using the QUADAS-2 tool for diagnostic studies.[9] We assessed their level of validation using the guideline proposed by the Evidence-Based Working Group[10] with one added category as described by Reilly,[11] ranging from level 1 'derivation of the model without validation' to level 5 'proven by broad impact analysis'.

Validation study

Validation populations

We retrospectively evaluated the validity of the identified prediction models in two study populations.[12,13] Population 1 included 248 children aged 1 month to 5 years presenting at the ED in 2012-2013 with fever and cough or dyspnoea, from a prospective study at the Erasmus MC - Sophia, Rotterdam, the Netherlands.[12] Population 2 included 301 children aged 3 months to 5 years presenting with fever and respiratory symptoms at a paediatric assessment unit at the University Hospitals Coventry and Warwickshire NHS Trust, United Kingdom (UK), in 2005-2006.[13] In both databases children with comorbidity related to increased risk of bacterial infection or complications were excluded, such as severe neurological impairment, immunodeficiency and severe pulmonary or cardiac defects. Follow-up was available for both populations, reducing the risk of missing (untreated) serious infections. The studies in these populations were approved by the Medical Ethics Committee of the Erasmus MC (Rotterdam) and the Coventry Local Research Ethics Committee. Written informed consent was obtained for both populations.[12,13]

Reference standard

As chest x-ray is no longer recommended as a gold standard in clinical practice, the diagnosis of bacterial pneumonia is mostly a clinically based diagnosis. A model that may reflect this clinical approach, is an algorithm published by Herberg et.al., classifying the potential

aetiology of febrile illness in children.[14] For this study, we used a reference standard adapted to this model, classifying patients' cause of respiratory tract infection from bacterial to viral (see S1 Figure). First, we pre-specified what working diagnosis would be classified as 'bacterial syndrome', 'viral syndrome' or 'unknown bacterial/viral', the first step of the algorithm. Then we categorized all patients based on their working diagnosis as documented in the different databases. We used the working diagnosis that was attributed by the attending clinician at the end of the ED visit, based on patient assessment and routine diagnostic tests. As a second step, we used identification of bacteria or viruses and CRP-level (>60 mg/l or ≤60mg/l) to further differentiate the clinical diagnosis. Diagnostic tests from routine care included viral PCR of nasopharyngeal swab and blood cultures, as performed at the discretion of the clinician. Given a low number of pathogens identified we had few definite diagnoses, so we classified patients into to five categories: definite or probable bacterial (1), bacterial syndrome (2), unknown bacterial or viral (3), viral syndrome (4) and definite or probable viral (5). For example, a child presenting with bronchiolitis (viral syndrome at first step), no virus or bacteria identified and a CRP-level of >60mg/l would be classified as having a viral syndrome. A child with a working diagnosis of pneumonia (unknown viral/bacterial at first step), the CRP-level would lead to either bacterial syndrome (in case of high CRP), viral syndrome (in case of low CRP) or remain unknown bacterial/viral (in case of no CRP performed). Patients with a bacterial and viral co-infection were classified as bacterial infection, given the consequences for treatment.

Statistical analysis

Missing data and outliers

Missing values were imputed 10 times using the mice package in R (version 3.3.2), resulting in 10 separate datasets with complete (imputed) information. The imputation model included information about clinical signs and symptoms, referral, diagnostic tests and treatment. We performed all analyses of the validation on the 10 imputed datasets and then averaged the results.[15] When a variable of a prediction model was completely missing in our database, multiple imputation was not possible and we used a proxy (e.g. 'retractions' as a proxy variable for 'dyspnoea', if 'dyspnoea' was not available). For continuous variables, the prevalence of that variable in the original derivation population of the prediction model was used (mean imputation).[16] CRP-level was truncated at the level of 225 mg/L, following the study of Nijman.[17]

Evaluation of validity of prediction models

We evaluated the validity of those prediction models of which more than 50% of the predictors were available in our database, assuming this as a minimum for credible

predictions.[16] We calculated the risk of bacterial pneumonia using each of the included prediction models for all children in our study populations, illustrated by histograms and boxplots. To measure performance, we calculated the ordinal c-statistic (ORC) – a measure similar to the area under the receiver-operating-curve (AUC), but for ordinal instead of dichotomous outcomes. This statistic can be interpreted as the probability that two cases of randomly selected outcome categories are correctly ranked.[18] We defined models with an ORC of at least 0.55 as performing well and explored their potential to guide antibiotic prescription. For this purpose, we evaluated the harms and benefits of withholding antibiotics in low-risk patients, compared to the observed usual care in which treatment decisions were based on clinical judgment and routine diagnostic tests. Benefit was defined as the potential reduction of antibiotic prescription and harm as the potential risk of under treatment. Under treatment was defined as children that were classified as having a bacterial infection and who had been treated with antibiotics, but whom the prediction model classified as low-risk. We explored different thresholds for the prediction models to define low-risk and evaluated their effect on harms and benefits. All analyses were performed using SPSS (IBM version 24.0) and R (version 3.3.2).

RESULTS

Identification, quality and original performance of prediction models

We identified 4324 unique articles (after removal of duplicates). Based on title and abstract 4176 articles were excluded as not relevant (see S2 Figure). After full-text selection and searching references, 11 articles were eligible for inclusion (see Table 1). Eight were primary derivation studies, describing different prediction models,[17,19-25] three were validation or impact studies of three of these models[12,26,27] and one derivation study also included the validation of another model.[25] Even though VandenBruel's model was derived mainly in general practice setting, it was also validated in an ED setting, and therefore included in our study. Most studies included children up to the age of 16, but the majority of the included patients in all studies were under five. Most studies had radiographic pneumonia as their reference standard, except for VandenBruel's study that used hospitalization for radiographic pneumonia as its reference standard (Table 1). All prediction models aimed to improve clinical decision-making in the child suspected of bacterial pneumonia. Three studies mainly focused on decisions on diagnostic tests;[19,21,23] the other studies also mentioned the potential of the models to improve management decisions on antibiotic treatment, admission or referral.[17,20,22,24,25]

In general the quality of the prediction models was moderate (see Table 1 and S3 Figure) with 3 models having some risk of bias[19,21,24] and one study with concerns about the applicability.[20] Nijman's model was evaluated most thoroughly including impact analysis.[17] The models by VandenBruel, Lynch and Oostenbrink were broadly validated in previous studies;[19,20,24] those by Mahabee-Gittens, Neuman, Craig and Irwin were only derived or validated in one setting by the original authors.[21-23,25]

Three prediction models provided a risk classification (high versus low risk), based on the presence of specific symptoms.[20,21,23] Of these models, sensitivity at model development was moderate to good, with varying specificity (see Table 1). Only VandenBruel's model was validated in different settings, performing poorly due to high sensitivity and low specificity in three settings, the opposite in another setting, and in a last setting both poor sensitivity and specificity.[26] The other four prediction models provided a probability (predicted risk in %) of pneumonia, based on a multiple logistic regression model.[17,19,24,25] These models showed moderate to good performance at development (AUC ranging from 0.67 to 0.84) as well as in the validation studies.[22,24,26]

Table 1. Characteristics of clinical prediction models

Clinical prediction rule	Setting	Population	Original reference standard	Prevalence pneumonia	Statistical model	Predictor variables	Performance				Level of evidence**	QUADAS-2
Risk classification (high versus low risk)							*Sensitivity*	*Specificity*	*LR+*	*LR-*		*risk of bias / concern applicability*
1. Mahabee (2005)[23]	US	2m - 5y, cough + 1 of following: labored/ rapid/ noisy breathing; chest/abdominal pain; fever	radiographic pneumonia	44/510 (8.6)	MLRM	age≥12 months, respiratory rate ≥50/ min, oxygen saturation ≤96%, nasal flaring in age <12months	63.6	77	2.8	0.5	1	low / low
2. Bruel, van den (2007)[20]	BE*	< 17y, acute illness	hospital admission for radiographic pneumonia	15/3981 (0.4)	CART	dyspnea, 'something is wrong'	93.8	93.2	13.9	0.07	3	low / high
Verbakel (validation 1, 2013)[26]	NL	"	"	17/506 (3.3)			94.1	44.6	1.7	0.13		
Verbakel (validation 2, 2013)	UK	"	"	131/2687 (4.9)			92.4	41.4	1.58	0.18		
Verbakel (validation 3, 2013)	NL	"	"	114/1750 (6.5)			65.8	43.1	1.16	0.79		NA, different datasets
Verbakel (validation 4, 2013)	NL	"	"	54/595 (9.1)			81.5	45.5	1.49	0.41		
Verbakel (validation 5, 2013)	UK	"	"	67/700 (9.6)			26.9	89.1	2.46	0.82		
3. Neuman (2011)[21]	US	< 21, chest X-ray for suspected pneumonia	radiographic pneumonia	422/2574 (16.4)	CART	oxygen saturation ≤92%, history of fever, wheezing, focal rales, chest pain, focal decreased breath sounds	90.1	21.6	1.2	0.4	1	some / low

Table 1. (continued)

Clinical prediction rule	Setting	Population	Original reference standard	Prevalence pneumonia	Statistical model	Predictor variables	Performance	Level of evidence**	QUADAS-2
Probability (predicted risk in %)							*AUC*		
4. Lynch (2004)[19]	US	1-16y, chest X-ray for suspected pneumonia	radiographic pneumonia	204/570 (35.8)	MLRM	fever, decreased breath sounds, crackles, tachypnea	0.67	3	some / low
Bilkis (validation, 2010)[27]	US	"		179/257 (69.6)			0.7		some / some
5. Oostenbrink (2013)[24]	NL	1m - 16y, fever and cough	nodular infiltration or consolidation on radiograph / rule out pneumonia by noneventful followup / consensus	78/504 (15.5)	MLRM	ill appearance, tachypnea, O2 <94%, CRP	0.79	3	some / low
Oostenbrink (validation 1, 2013)	NL	"		58/420 (13.8)			0.81		
Oostenbrink (validation 2, 2013)	NL	"		27/366 (7.4)			0.86		

Table 1. (continued)

Clinical prediction rule	Setting	Population	Original reference standard	Prevalence pneumonia	Statistical model	Predictor variables	Performance	Level of evidence**	QUADAS-2
6. Craig (2010)[22]	AU	<5y, fever	consolidation on radiograph	533/15781 (3.4)	MLRM	general appearance, cough, temperature, breathing difficulty, abnormal chest sounds, chronic disease, capillary refill time, urinary symptoms, elevated respiratory rate, crackles, pneumococcal vaccine status, elevated heart rate, felt hot, meningococcal vaccine state, infectious contacts, crying, fluid intake, respiratory symptoms, diarrhoea, bulging fontanelle, male sex, focal bacterial infection, abnormal ear/ nose/throat signs, age, rash, stridor, wheeze	0.84	2	low / low
Craig (validation, 2010)	AU	"		193/5584 (3.5)			0.84		low / low

Table 1. (continued)

Clinical prediction rule	Setting	Population	Original reference standard	Prevalence pneumonia	Statistical model	Predictor variables	Performance	Level of evidence**	QUADAS-2
7. Nijman (2013)[17]	NL	1m - 15y, fever	nodular infiltration or consolidation on radiograph; rule out pneumonia by noneventful followup	171/2717 (6.3)	MLRM	age, sex, duration of fever, temperature, respiratory rate, heart rate, oxygen saturation, capillary refill, retractions, ill appearance, CRP	0.81	4	low / low
Nijman (validation, 2013)	NL	"		59/487 (12.1)			0.81		low / low
De Vos (validation, 2015) [12]	NL	"		33/439 (7.5)			0.83		low / low
8. Irwin (2017)[25]	US	<16y, (history of) fever	respiratory symptoms, signs and focal consolidation on radiograph	63/532 (12)	MLRM	CRP, respiratory rate, normal air entry, resistine, procalcitonin	0.84	1	low / low

m = months, y = years, ED = emergency department, GP = general practice, US = United States of America, BE = Belgium, NL = the Netherlands, AU = Australia, UK = United Kingdom CART = classification and regression tree, MLRM = multivariable linear regression model, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, AUC = area under the receiver operating curve, [a]derived in general practice and emergency department, validated in ED, [b]as described by Reilly (range 1 (only derived) to 5 (proven by broad impact analysis)[11]

Validation study

Table 2 shows the baseline characteristics of the two populations. Using the clinical diagnosis, bacterial infection rate ranged from 9-17% and 38-41% were classified as 'unknown'. Of this latter category 74-87% recovered without antibiotics. We included seven prediction models in our validation study. We did not assess validity of Craig's model as only 14/28 variables were present in both databases. Lynch – having only 2/4 variables available – was not validated in the Coventry database. The supplementary S1 Table gives an overview of all variables and proxies of the validated prediction models. Mahabee-Gittens published a regression model providing a probability, but the coefficients to calculate this probability were not available from the author [23]. We therefore used the presence of one or more of the included variables classifying patients at high risk of bacterial pneumonia. VandenBruel published a general prediction model for febrile children, and one for pneumonia; for this review we only used the pneumonia model [20]. Neuman used a decision tree to classify patients into 3 categories (high/intermediate/low risk of pneumonia) [21]. In this model 'history of fever' discriminated intermediate from low risk, but since fever was an inclusion criteria of all our validation populations, only high and low risk patients were identified, based on the first step of the decision tree (oxygen saturation <92%).

Table 2. Baseline characteristics of validation populations.

	Rotterdam, n=248	**Coventry, n=301**
Predictor variables	*median (IQR) or n(%)*	*median (IQR) or n(%)*
Age (months)	14 (7-27)	19 (12-31)
Gender (male)	148/248 (60%)	174/301 (58%)
Temperature (C°)	38.2 (37.4-39.1)	38.2 (37.5-39.1)
Duration of fever (days)	3 (2-4)	not available
Tachypnea	81/183 (44%)	154/258 (60%)
Tachycardia	66/207 (32%)	191/294 (65%)
Oxygen saturation (%)	98 (97-100)	97 (95-98)
Ill appearance	35/149 (23%)	1/301 (0%)
Dyspnoea	106/248 (43%)	81/301 (27%)
Decreased breath sounds	12/136 (9%)	not available
Crackles	30/127 (24%)	not available
Focal rales	67/151 (44%)	not available
Retractions	68/107 (64%)	not available
Nasal flaring	29/58 (50%)	not available
Prolonged capillary refill (>2sec)	10/53 (19%)	58/187 (31%)

Table 2. (continued)

	Rotterdam, n=248	Coventry, n=301
Diagnostics and treatment		
CRP measured	94/248 (38%)	109/301 (36%)
CRP (mg/L)	16 (7-42)	45 (19-122)
X-ray performed	42/248 (17%)	67/301 (22%)
Antibiotics prescribed	51/248 (21%)	105/301 (35%)
Clinical diagnosis (S1 Figure)		
Definite or probable bacterial	18/248 (7%)	37/301 (12%)
Bacterial syndrome	4/248 (2%)	16/301 (5%)
Unknown	94/248 (38%)	122/301 (41%)
Viral syndrome	59/248 (24%)	72/301 (24%)
Definite or probable viral	73/248 (29%)	54/301 (18%)

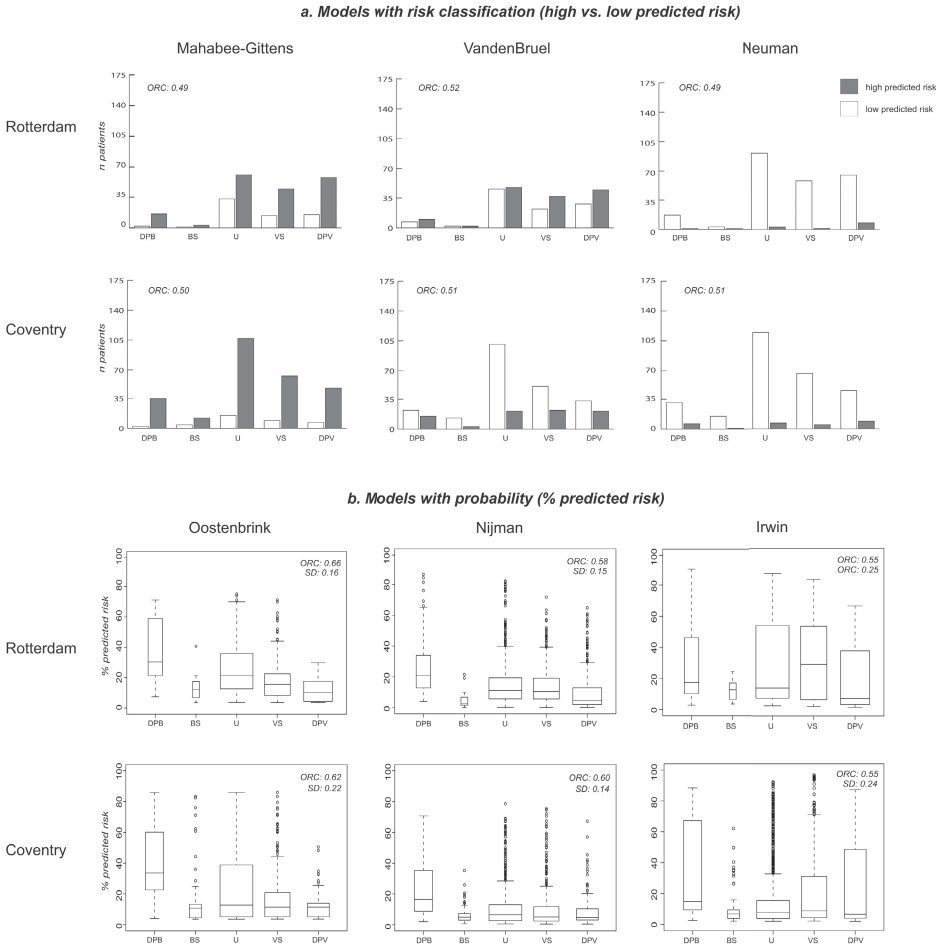
IQR = interquartile range

Performance of prediction models

The performance of the three models with a risk classification (high/low risk) is shown in Figure 1a. The white bars indicate the number of children with predicted low risk of pneumonia and the grey bars the number of patients with predicted high risk, across the five reference standard categories (bacterial to viral infection). For example, when we used Mahabee-Gittens' model to predict the risk of having a bacterial pneumonia in our two validation populations, we observed that this model predicts most children as having a high risk of pneumonia (grey bars), including most children with viral infections. Using VandenBruel's model, we observed low as well as high predicted risks across all 5 diagnosis categories. Almost all children were assigned to a low risk group using Neuman's model, including children with bacterial infections.

Figure 1b shows the performance of the prediction models providing a probability. Again, predictions are shown across the five diagnosis categories for each model and for both populations, illustrated by a boxplot. Lynch's model predicted high risk of pneumonia (around 90%) for all children, with little variation across the different outcome categories (see S4 Figure), and did not contribute to discrimination between bacterial or viral disease. The models by Oostenbrink, Nijman and Irwin assigned higher risks to children with bacterial infections than to the children with viral infections, confirmed by a moderate ordinal c-statistic of ≥0.55 (see Figure 1b).

Figure 1. Performance of prediction models.



Footnote:
DPB = definite or probable bacterial, BS = bacterial syndrome, U = unknown, VS = viral syndrome, DPV = definite or probable viral; ORC = ordinal c-statistic; SD = standard deviation;

To assess the clinical relevance of these findings, we explored the potential of the last three models to define low-risk patients possibly not needing antibiotic treatment. For example, applying a risk threshold of 10% using Nijman's model would classify 130 children (52%) in the Rotterdam population as being at low risk of bacterial pneumonia (see Table 3, details in S2 Table). Of these children 16 were currently treated with antibiotics. If this threshold would be used in clinical practice, and antibiotics would be withheld in all low-risk children, the overall antibiotic prescription rate would reduce from 21% (observed antibiotic prescription) to 14% (expected antibiotic prescription) in the Rotterdam population and from 35% to 16%

in the Coventry population (Table 3). The potential risk of under treatment (e.g. withholding antibiotics in children with a bacterial infection who were currently treated with antibiotics) would be 2% (Rotterdam) and 5% (Coventry). Similar benefits and harms were observed when applying the models of Oostenbrink and Irwin. A threshold of 15% would lead to greater reduction in antibiotic prescription, but at a higher risk of under treatment.

Table 3. Clinical consequences of using prediction models to guide antibiotic prescription

	Rotterdam, n=248	**Coventry, n=301**
Observed antibiotic prescription, n (%)	51 (21%)	105 (35%)
Predictions by Nijman's model		
Threshold 10%	*Rotterdam*	*Coventry*
Number of children below threshold **(low-risk group)**	130 (52%)	193 (64%)
Expected antibiotic prescription when guided by threshold **(benefit)**	35 (14%)	49 (16%)
Expected under treatment when prescription was guided by threshold **(harm)**[a]	5 (2%)	15 (5%)
Threshold 15%		
Number of children below threshold	167 (67%)	229 (76%)
Expected antibiotic prescription when guided by threshold	28 (11%)	36 (12%)
Expected under treatment when prescription was guided by threshold	8 (3%)	22 (7%)
Predictions by Oostenbrink's model		
Threshold 10%	*Rotterdam*	*Coventry*
Number of children below threshold	69 (28%)	94 (31%)
Expected antibiotic prescription when guided by threshold	44 (18%)	77 (26%)
Expected under treatment when prescription was guided by threshold	0 (0%)	8 (3%)
Threshold 15%		
Number of children below threshold	110 (44%)	178 (59%)
Expected antibiotic prescription when guided by threshold	35 (14%)	51 (17%)
Expected under treatment when prescription was guided by threshold	2 (1%)	13 (4%)
Predictions by Irwin's model		
Threshold 10%	*Rotterdam*	*Coventry*
Number of children below threshold	100 (40%)	155 (51%)
Expected antibiotic prescription when guided by threshold	38 (15%)	64 (21%)
Expected under treatment when prescription was guided by threshold	5 (2%)	15 (5%)
Threshold 15%		
Number of children below threshold	120 (48%)	198 (66%)
Expected antibiotic prescription when guided by threshold	33 (13%)	48 (16%)
Expected under treatment when prescription was guided by threshold	8 (3%)	22 (7%)

[a] *Number of children with a bacterial infection who were treated with antibiotics, but who were classified as low-risk according to the used prediction model and threshold*

DISCUSSION

We identified eight clinical prediction models for childhood pneumonia by literature review. Following changing perspectives on a relevant reference standard for childhood pneumonia, we could assess the validity of seven of them for a clinical diagnosis of bacterial, unknown bacterial/viral or viral infection. Three models – with good original performance and quality – assigned a higher risk to children with bacterial infection than to those with viral infection, with the potential of proper selection of children who may recover without antibiotics.

An important strength of our study is the broad validation of multiple prediction models in prospective cohorts including over 500 patients in two different European acute care settings. Our populations were rather heterogeneous in terms of their clinical characteristics, increasing the generalizability of our findings. A limitation is the heterogeneity of the information available, and missing values in general, which is related to the use of already existing datasets. We have accounted for this by multiple imputation or by using proxies where possible. Another limitation is the retrospective classification of the clinical diagnosis, based on the working diagnosis by the treating physician not blinded for clinical features and diagnostic tests. Because none of these clinical features or tests alone determined classification into a final diagnosis category, we believe this potential bias is limited. Diagnostic tests were performed at the discretion of the treating clinician, and included chest x-rays mainly. For 22 patients a definite viral or bacterial test was recorded to be positive, however, we had no data on the total performed viral/bacterial tests. Previous studies in these settings have shown that these are performed in about 10% of febrile children.[12,13] Validity assessment of the model by Mahabee-Gittens was limited by the absence of the original coefficients. Of Irwin's model only 3 out of 5 predictor variables were present, for the other two variables we used mean imputation. This may have underestimated the model's discriminative value; but given the small effect sizes of the missing variables, we consider this effect limited.[16]

We should appreciate several differences between our study populations and the populations the models were originally derived on. Since our populations included febrile children at the ED, it is not surprising that we observed less variability in the predicted probabilities in the validation of Neuman and Lynch' models, since fever was one of their predictor variables. Furthermore, differences in pneumonia prevalence in the derivation populations (6-36%) of the models may explain systematic differences in predicted probabilities in 4 models.[17,19,24,25,28] In general, correcting for this involves recalibration (calibration-in-the-large) of the model to a new target population.[28] However, this type of recalibration does not influence discrimination (the ordinal c-statistic), and thus not our conclusions. It may, however, explain the variable

impact the suggested thresholds have using the different models. Next, the type of reference standard (radiographic pneumonia vs. clinical diagnosis) differed between derivation and validation studies, as was the purpose of our study. Given the diagnostic limitations of chest X-rays, we chose to define our reference standard following Herberg's classification.[14] It must be noted that this choice was not proposed as a new gold standard, but rather used as a model that may reflect our best current practice. In our aim to translate prediction models into clinical practice, we observed that the performance varied by type of model. We observed that the models using the probability scale had better diagnostic performance (reflected by a higher ORC statistic) than those using a risk classification (high/low risk). This can partly be explained by the ability to adjust risk thresholds – with a direct link to the harm-benefit ratio – more easily in models using the probability scale. Models using a risk classification have a fixed threshold and lack this flexibility and may therefore show lower diagnostic performance when validated according to a new reference standard.

In order to improve rational use of antibiotics in children with respiratory infections, there is a need to improve discrimination between bacterial and viral, self-limiting disease. We showed that three of seven tested clinical prediction models could identify a low-risk group of children with self-limiting disease in an ED population fairly well and we believe those three have the potential to improve treatment decisions. Those models include a combination of signs of general illness and/or respiratory distress and biomarkers. The availability of biomarkers will influence the feasibility of implementation of these models in clinical practice. The models of Oostenbrink and Nijman include CRP measurement, Irwin's model includes CRP, procalcitonin and resistin. Given the wide availability of point-of-care CRP tests the first two models will be most feasible for routine use in the ED.

Another important challenge to be faced before prediction models can be implemented as decision tools in clinical practice is to choose optimal decision thresholds, adapted to the appropriate target population. A balance is needed between the benefit of reducing unnecessary antibiotic prescription and the harm of potential under treatment of bacterial infections. The prior risk of severe illness in a population is an important consideration. For example, in settings with high prevalence of comorbidity, the course of pneumonia will generally be more severe and missing a serious infection will have worse consequences than in a low-risk population. Next, the natural course of the disease should be taken into account. Last, access to (good quality) healthcare is important. In a setting with limited possibility for patient follow-up, potential risks of under treatment will higher. Given the natural course of pneumonia (developing over days instead of hours), a watchful waiting approach instead of immediate antibiotic treatment in children with uncomplicated pneumonia with a predicted

risk <10-15% might be justified in settings with good access to care, in the presence of a proper safety-netting strategy for unexpected disease course. In low resource settings or high-risk populations lower thresholds may be reasonable. Before implementing treatment interventions based on these prediction models in clinical practice, a prospective study is needed to evaluate the overall impact of treating children according to such a prediction model, compared to usual care. Such a study should assess the feasibility and safety of the suggested thresholds for that specific setting.

Three out of seven clinical prediction models for pneumonia could discriminate fairly well between a new reference standard of bacterial and viral infection in children presenting at the ED. However, they all require the measurement of biomarkers, raising questions on the exact target population when implementing these models in clinical practice. Moreover, choosing optimal decision to guide antibiotic prescription is challenging and requires careful consideration of potential harms and benefits. Future research should focus on the feasibility and safety of treatment based on chosen decision thresholds for specific settings.

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Supporting information

S1 Text. Search strategy and in/exclusion criteria for systematic review

Original search strategy, April 2016

Database	Number of articles	Number of articles after deleting duplicates
Embase.com	2676	2646
Medline Ovid	1466	310
Web of science	1462	610
PubMed publisher	52	31
Google scholar	223	158
Total	**5879**	**3755**

Embase.com 2676

('pneumonia'/exp OR (pneumoni* OR Bronchopneumoni* OR Pleuropneumoni*):ab,ti OR (('respiratory tract infection'/de OR 'lower respiratory tract infection'/de OR 'viral respiratory tract infection'/de OR (((respirator* NEAR/6 infection*) NOT (upper NOT lower))):ab,ti) AND ('antibiotic agent'/exp OR (antibiotic*):ab,ti))) AND ('practice guideline'/exp OR 'decision making'/exp OR 'decision support system'/exp OR 'decision tree'/exp OR ((guideline* OR ((decision OR prediction*) NEAR/3 (making OR support* OR tree* OR model* OR model* OR algorithm* OR triage* OR protocol* OR principle* OR aid OR aids))):ab,ti OR ((guideline* OR decision* OR model OR tree OR prediction* OR model* OR algorithm* OR triage* OR protocol* OR principle*) NEAR/6 (develop* OR propose* OR new OR novel OR validat* OR Evaluat* OR implement* OR modif*)):ab,ti)) AND (child/exp OR 'pediatrics'/de OR (preschool* OR child* OR schoolchild* OR infan* OR toddler* OR pediatric* OR paediatric*):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

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(exp "pneumonia"/ OR (pneumoni* OR Bronchopneumoni* OR Pleuropneumoni*).ab,ti. OR (("Respiratory Tract Infections"/ OR (((respirator* ADJ6 infection*) NOT (upper NOT lower))).ab,ti.) AND ("antibiotic agent"/ OR (antibiotic*).ab,ti.))) AND (exp "guideline"/ OR exp "Decision Making"/ OR "Decision Support Systems, Clinical"/ OR "Decision Support Techniques"/ OR "Decision Trees"/ OR ((guideline* OR ((decision OR prediction*) ADJ3 (making OR support* OR tree* OR model* OR model* OR algorithm* OR triage* OR protocol* OR principle* OR aid OR aids))).ab,ti. OR ((guideline* OR decision* OR model OR tree OR prediction* OR model* OR algorithm* OR triage* OR protocol* OR principle*) ADJ6 (develop* OR propose* OR new OR novel OR validat* OR Evaluat* OR implement* OR modif*)).ab,ti.)) AND (exp child/ OR infant/ OR "pediatrics"/ OR (preschool* OR child* OR schoolchild* OR infan* OR toddler* OR pediatric* OR paediatric*).ab,ti.) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Web of science 1462

TS=(((pneumoni* OR Bronchopneumoni* OR Pleuropneumoni*) OR (((((respirator* NEAR/5 infection*) NOT (upper NOT lower)))) AND ((antibiotic*))))) AND (((guideline* OR ((decision OR prediction*) NEAR/2 (making OR support* OR tree* OR model* OR model* OR algorithm* OR triage* OR protocol* OR principle* OR aid OR aids))) OR ((guideline* OR decision* OR model OR tree OR prediction* OR model* OR algorithm* OR triage* OR protocol* OR principle*) NEAR/5 (develop* OR propose* OR new OR novel OR validat* OR Evaluat* OR implement* OR modif*)))) AND ((preschool* OR child* OR schoolchild* OR infan* OR toddler* OR pediatric* OR paediatric*))) AND LA=(english) AND DT=(article)

PubMed publisher 52

("pneumonia"[mh] OR (pneumoni*[tiab] OR Bronchopneumoni*[tiab] OR Pleuropneumoni*[tiab]) OR (("Respiratory Tract Infections"[mh] OR (((respirator*[tiab] AND infection*[tiab]) NOT (upper[tiab] NOT lower[tiab])))) AND ("antibiotic agent"[mh] OR (antibiotic*[tiab])))) AND ("guideline"[mh] OR "Decision Making"[mh] OR "Decision Support Systems, Clinical"[mh] OR "Decision Support Techniques"[mh] OR "Decision Trees"[mh] OR ((guideline*[tiab] OR ((decision[tiab] OR prediction*[tiab]) AND (making OR support*[tiab] OR tree*[tiab] OR model*[tiab] OR model*[tiab] OR algorithm*[tiab] OR triage*[tiab] OR protocol*[tiab] OR principle*[tiab] OR aid[tiab] OR aids[tiab]))) OR ((guideline*[tiab] OR decision*[tiab] OR model[tiab] OR tree[tiab] OR prediction*[tiab] OR model*[tiab] OR algorithm*[tiab] OR triage*[tiab] OR protocol*[tiab] OR principle*[tiab]) AND (develop*[tiab] OR propose*[tiab] OR new OR novel OR validat*[tiab] OR Evaluat*[tiab] OR implement*[tiab] OR modif*[tiab])))) AND (child[mh] OR infant[mh] OR "pediatrics"[mh] OR (preschool*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infan*[tiab] OR toddler*[tiab] OR pediatric*[tiab] OR paediatric*[tiab])) AND english[la] NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR congresses[pt] OR abstracts[pt]) AND publisher[sb]

Google scholar First 200

Pneumonia guideline|"decision|prediction making|support|tree|model|model|aid|aids"
child|children|schoolchild|infants|pediatric|paediatric antibiotic|antibiotics|"anti biotic"

allintitle:Pneumonia guideline|"decision|prediction making|support|tree|model|model|aid|aids"
child|children|schoolchild|infants|pediatric|paediatric

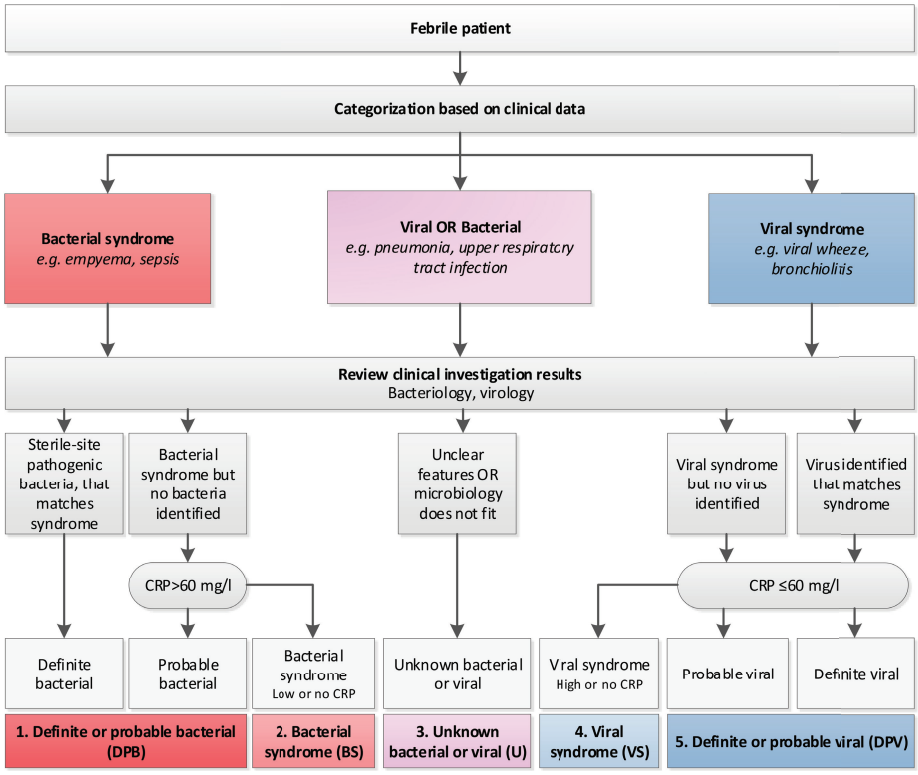
Update literature search, September 2017

Database	Number of articles	Number of articles after deleting duplicates
Embase.com	3092	3041
Medline Ovid	1763	369
Web of science	1730	726
Google scholar	200	150
Total	6785	4286

In- and exclusion criteria for systematic review

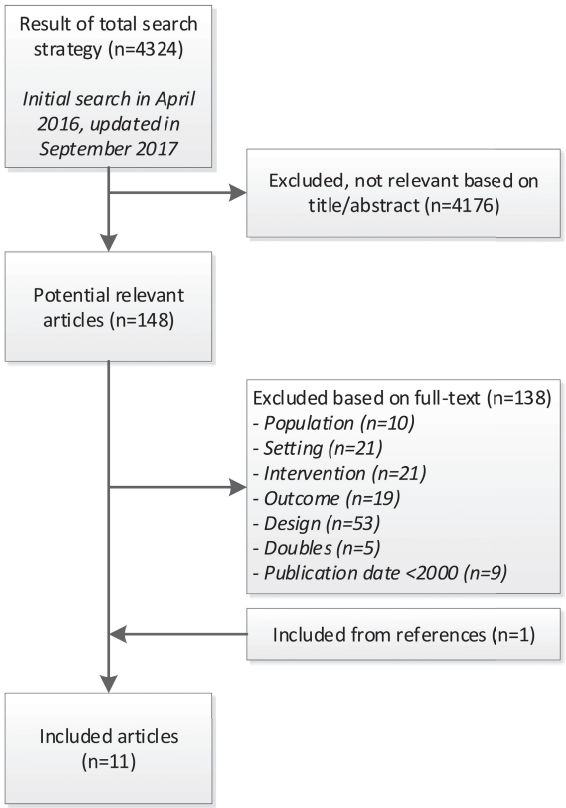
Characteristic	Inclusion	Exclusion
Design	Studies assessing diagnostic accuracy or deriving or validating prediction models	Reviews, conference abstracts, letters, notes, editorials, news, comments
Participants	Children aged 1month to 5 years are substantial part (>50%) of the population.	Out of age range, children with severe comorbidity
Setting	Developed countries (based on the United Nations classification) Emergency department	Developing countries Primary care, in-hospital setting
Intervention	Multifactor clinical prediction rule including clinical features (and biomarkers).	Rules without clinical features, or including tests not available at ED
Outcome	(bacterial) pneumonia treatment advice for pneumonia	Other diagnosis

S1. Figure. Classification of febrile illness.

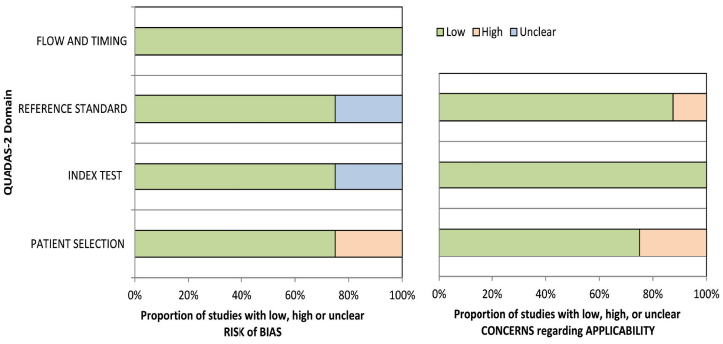


Based on Herberg et al.[14]

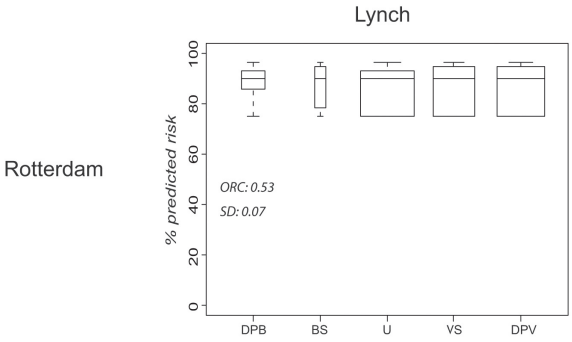
S2. Figure. Flowchart of the selection process.



S3. Figure. QUADAS-2 quality assessment.



S4. Figure. Performance Model Lynch.



DPB = definite or probable bacterial, BS = bacterial syndrome, U = unknown, VS = viral syndrome, DPV = definite or probable viral; ORC = ordinal c-statistic; SD = standard deviation

S1. Table. Missings and proxies of predictor variables.

	Rotterdam, n=248		**Coventry, n=301**	
Predictor variables	*Missing, n (%)*	*Proxy*	*Missing, n (%)*	*Proxy*
Age, months	none		none	
Gender	none		none	
Temperature (°C)	12 (5)		4 (1.3)	
Duration of fever (days)	189 (76)		301 (100)	Derivation population
Respiratory rate	65 (26)		43 (14)	
Heart rate	41 (17)		7 (2)	
Oxygen saturation (%)	76 (30)		15 (5)	
Ill appearance	99 (40)		none	Toxic appearance
Dyspnea	none			
Decreased breath sounds	112 (45)		301 (100)	NA
Crackles	121 (49)		301 (100)	NA
Focal rales	97 (39)		301 (100)	NA
Retractions	143 (57)		301 (100)	NA
Nasal flaring	190 (77)		301 (100)	Dyspnea
Prolonged capillary refill (>2sec)	53 (21)		114 (38)	
CRP, mg/L	154 (62)		192 (64)	
Normal air entry		Absence of dyspnea		Absence of dyspnea
Resistin, ng/mL	248 (100)	Derivation population	301 (100)	Derivation population
PCT, ug/L	248 (100)	Derivation population	301 (100)	Derivation population

NA = not assessed, no close proxy available

S2. Table. Detailed classification of risk groups based on different prediction models.

Nijman Rotterdam

Antibiotic prescription			Clinical diagnosis					Total
			DPB	BS	U	VS	DPV	
No	Predicted risk	0 - 10 %	0	2	40	28	44	114
		10 - 15%	0	0	15	11	4	30
		>15 %	0	0	27	19	7	53
	Total		0	2	82	58	55	197
Yes	Predicted risk	0 - 10 %	3	2	3	0	8	16
		10 - 15%	3	0	2	0	2	7
		>15 %	12	0	7	1	8	28
	Total		18	2	12	1	18	51
Threshold 10%				n	**%**			
Total number of children below threshold				130	**52%**			
Number of treated children below threshold				16	**6%**			
Number of treated children with bacterial infection below threshold				5	**2%**			
Antibiotic prescription when guided by threshold 10%				35	14%			
Threshold 15%								
Total number of children below threshold				167	**67%**			
Number of treated children below threshold				23	**9%**			
Number of treated children with bacterial infection below threshold				8	**3%**			
Antibiotic prescription when guided by threshold 15%				28	11%			

Nijman Coventry

Antibiotic prescription			Clinical diagnosis					Total
			DPB	BS	U	VS	DPV	
No	Predicted risk	0 - 10 %	4	4	67	41	21	137
		10 - 15%	1	0	15	6	1	23
		>15 %	3	0	20	11	2	36
	Total		8	4	102	58	24	196
Yes	Predicted risk	0 - 10 %	6	9	12	10	19	56
		10 - 15%	5	2	1	2	3	13
		>15 %	19	1	5	3	8	36
	Total		30	12	18	15	30	105
Threshold 10%								
Total number of children below threshold				193	**64%**			
Number of treated children below threshold				56	**19%**			
Number of treated children with bacterial infection below threshold				15	**5%**			
Antibiotic prescription when guided by threshold 10%				49	16%			
Threshold 15%								
Total number of children below threshold				229	**76%**			
Number of treated children below threshold				69	**23%**			
Number of treated children with bacterial infection below threshold				22	**7%**			
Antibiotic prescription when guided by threshold 15%				36	12%			

Oostenbrink Rotterdam

Antibiotic prescription			Clinical diagnosis					Total
			DPB	BS	U	VS	DPV	
No	Predicted risk	0 - 10 %	0	2	17	16	27	62
		10 - 15%	0	0	6	12	14	32
		>15 %	0	0	59	30	14	103
	Total		0	2	82	58	55	197
Yes	Predicted risk	0 - 10 %	0	0	1	0	6	7
		10 - 15%	2	0	1	0	6	9
		>15 %	16	2	10	1	6	35
	Total		18	2	12	1	18	51
Threshold 10%								
Total number of children below threshold				69	**28%**			
Number of treated children below threshold				7	**3%**			
Number of treated children with bacterial infection below threshold				0	**0%**			
Antibiotic prescription when guided by threshold 10%				44	18%			
Threshold 15%								
Total number of children below threshold				110	**44%**			
Number of treated children below threshold				16	**6%**			
Number of treated children with bacterial infection below threshold				2	**1%**			
Antibiotic prescription when guided by threshold 15%				35	14%			

Oostenbrink Coventry

Antibiotic prescription			Clinical diagnosis					Total
			DPB	BS	U	VS	DPV	
No	Predicted risk	0 - 10 %	1	2	33	22	8	66
		10 - 15%	1	2	24	19	12	58
		>15 %	5	0	46	17	4	72
	Total		7	4	103	58	24	196
Yes	Predicted risk	0 - 10 %	3	5	6	4	10	28
		10 - 15%	1	4	5	2	14	26
		>15 %	26	3	8	8	6	51
	Total		30	12	19	14	30	105
Threshold 10%								
Total number of children below threshold				94	**31%**			
Number of treated children below threshold				28	**9%**			
Number of treated children with bacterial infection below threshold				8	**3%**			
Antibiotic prescription when guided by threshold 10%				77	26%			
Threshold 15%								
Total number of children below threshold				178	**59%**			
Number of treated children below threshold				54	**18%**			
Number of treated children with bacterial infection below threshold				13	**4%**			
Antibiotic prescription when guided by threshold 15%				51	17%			

Irwin Rotterdam

Antibiotic prescription			Clinical diagnosis					Total
			DPB	BS	U	VS	DPV	
No	Predicted risk	0 - 10 %	0	1	29	19	38	87
		10 - 15%	0	0	11	4	0	15
		>15 %	0	1	42	35	17	95
	Total			2	82	58	56	197
Yes	Predicted risk	0 - 10 %	4	1	5	1	2	13
		10 - 15%	3	0	2	0	0	5
		>15 %	11	1	5	0	16	33
	Total		18	2	12	1	18	51
Threshold 10%					**%**			
Total number of children below threshold				100	**40%**			
Number of treated children below threshold				13	**5%**			
Number of treated children with bacterial infection below threshold				5	**2%**			
Antibiotic prescription when guided by threshold 10%				38	15%			
Threshold 15%								
Total number of children below threshold				120	**48%**			
Number of treated children below threshold				18	**7%**			
Number of treated children with bacterial infection below threshold				8	**3%**			
Antibiotic prescription when guided by threshold 15%				33	13%			

Irwin Coventry

Antibiotic prescription			Clinical diagnosis					Total
			DPB	BS	U	VS	DPV	
No	Predicted risk	0 - 10 %	3	3	58	32	18	114
		10 - 15%	2	0	19	5	1	27
		>15 %	2	1	26	21	5	55
	Total		7	4	103	58	24	196
Yes	Predicted risk	0 - 10 %	7	8	10	3	13	41
		10 - 15%	6	1	3	5	1	16
		>15 %	17	3	6	6	16	48
	Total		30	12	19	14	30	105
Threshold 10%								
Total number of children below threshold				155	**51%**			
Number of treated children below threshold				41	**14%**			
Number of treated children with bacterial infection below threshold				15	**5%**			
Antibiotic prescription when guided by threshold 10%				64	21%			
Threshold 15%								
Total number of children below threshold				198	**66%**			
Number of treated children below threshold				57	**19%**			
Number of treated children with bacterial infection below threshold				22	**7%**			
Antibiotic prescription when guided by threshold 15%				48	16%			

Chapter 3.2.

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

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ABSTRACT

Background

Optimising the use of antibiotics is a key component of antibiotic stewardship. Respiratory tract infections (RTIs) are the most common reason for antibiotic prescription in children, even though most of these infections in children under 5 years are viral. This study aims to safely reduce antibiotic prescriptions in children under 5 years with suspected lower RTI at the emergency department (ED), by implementing a clinical decision rule.

Methods and findings

In a stepped-wedge cluster randomised trial, we included children aged 1–60 months presenting with fever and cough or dyspnoea to 8 EDs in The Netherlands. The EDs were of varying sizes, from diverse geographic and demographic regions, and of different hospital types (tertiary versus general). In the pre-intervention phase, children received usual care, according to the Dutch and NICE guidelines for febrile children. During the intervention phase, a validated clinical prediction model (Feverkidstool) including clinical characteristics and C-reactive protein (CRP) was implemented as a decision rule guiding antibiotic prescription. The intervention was that antibiotics were withheld in children with a low or intermediate predicted risk of bacterial pneumonia (≤10%, based on Feverkidstool). Co-primary outcomes were antibiotic prescription rate and strategy failure. Strategy failure was defined as secondary antibiotic prescriptions or hospitalisations, persistence of fever or oxygen dependency up to day 7, or complications. Hospitals were randomly allocated to 1 sequence of treatment each, using computer randomisation. The trial could not be blinded. We used multilevel logistic regression to estimate the effect of the intervention, clustered by hospital and adjusted for time period, age, sex, season, ill appearance, and fever duration; predicted risk was included in exploratory analysis. We included 999 children (61% male, median age 17 months [IQR 9 to 30]) between 1 January 2016 and 30 September 2018: 597 during the pre-intervention phase and 402 during the intervention phase. Most children (77%) were referred by a general practitioner, and half of children were hospitalised. Intention-to-treat analyses showed that overall antibiotic prescription was not reduced (30% to 25%, adjusted odds ratio [aOR] 1.07 [95% CI 0.57 to 2.01, p = 0.75]); strategy failure reduced from 23% to 16% (aOR 0.53 [95% CI 0.32 to 0.88, p = 0.01]). Exploratory analyses showed that the intervention influenced risk groups differently (p < 0.01), resulting in a reduction in antibiotic prescriptions in low/intermediate-risk children (17% to 6%; aOR 0.31 [95% CI 0.12 to 0.81, p = 0.02]) and a non-significant increase in the high-risk group (47% to 59%; aOR 2.28 [95% CI 0.84 to 6.17, p = 0.09]). Two complications occurred during the trial: 1 admission to the intensive care unit during follow-up and 1 pleural empyema at day

10 (both unrelated to the study intervention). Main limitations of the study were missing CRP values in the pre-intervention phase and a prolonged baseline period due to logistical issues, potentially affecting the power of our study.

Conclusions

In this multicentre ED study, we observed that a clinical decision rule for childhood pneumonia did not reduce overall antibiotic prescription, but that it was non-inferior to usual care. Exploratory analyses showed fewer strategy failures and that fewer antibiotics were prescribed in low/intermediate-risk children, suggesting improved targeting of antibiotics by the decision rule.

Trial registration

Netherlands Trial Register NTR5326

INTRODUCTION

Respiratory tract infections (RTIs) are the most common diagnosis in febrile children, and the most common reason for antibiotic prescription in children.[1] In children under 5 years, most lower RTIs are viral.[2] Although mortality caused by lower RTIs has decreased significantly over the past decades (currently 1.7 per 100,000 people in Western Europe),[3] antimicrobial resistance due to unnecessary antibiotic prescription is increasing.[4] High variability in antibiotic prescription in children with RTIs in primary as well as hospital care throughout Europe highlights the need for better targeting of antibiotic prescriptions in this patient group.[1,5,6]

One of the main challenges when attempting to safely reduce antibiotic prescriptions for lower RTIs in children is the absence of a gold standard for the diagnosis of bacterial pneumonia. Routine chest X-rays are no longer recommended for the differentiation between bacterial and viral causes, and treatment decisions are mostly based on clinical findings.[7,8] Ongoing research into new biomarkers has not yet provided a new gold standard for clinical practice in the emergency department (ED).[9-11] In the absence of a gold standard for diagnosing bacterial pneumonia, we need to improve the clinical detection rate of those children who may benefit most from antibiotic treatment of bacterial pneumonia. Clinical prediction models combining clinical characteristics and biomarkers may improve the identification of children who will benefit from antibiotic treatment for community-acquired pneumonia, but they are not used as decision rules in clinical practice.[12,13] The Feverkidstool is a clinical prediction model combining clinical characteristics and C-reactive protein (CRP) to predict the risk of bacterial pneumonia and other serious bacterial infections in children. The model was derived in the ED setting in The Netherlands, and its diagnostic accuracy has been proven in external validation studies in The Netherlands and the United Kingdom.[13,14]

In this study we evaluated the impact of the Feverkidstool on clinical practice, as a last step in the development of a prediction model.[15] We translated the Feverkidstool into a decision rule with pre-specified decision thresholds to guide antibiotic treatment for lower RTIs. The primary objective of this study was to safely reduce antibiotic prescription in children under 5 years with suspected lower RTI at the ED, by withholding antibiotics in children at low or intermediate risk of bacterial pneumonia, as predicted by the Feverkidstool.

METHODS

Study design

We performed a stepped-wedge cluster randomised trial with sequential implementation of a treatment strategy for antibiotic prescription based on a clinical decision rule (hereafter called 'decision rule') in febrile children with suspected lower RTI in the ED. Randomisation at cluster level was chosen to avoid contamination of the intervention effect to control patients. The stepped-wedge design was preferred as, in general, smaller sample sizes are needed than in conventional cluster randomised trials. Because clusters act as their own controls, the intervention effect can be estimated from both between and within cluster comparisons. The sequential implementation of the intervention was deemed superior to a conventional before–after design, given the incorporation of time effects.[16] We performed the trial in 8 clusters (hospitals) between 1 January 2016 and 30 September 2018 in The Netherlands. By design, the trial consisted of 2 phases: a pre-intervention phase, when usual care was provided, and an intervention phase, wherein care was provided according to our intervention (diagram of trial design in Fig 1). A cluster consisted of 1 hospital that was randomised to 1 sequence of treatment. Each hospital was randomised to 1 sequence of treatment, resulting in 8 sequences. The period when all hospitals still performed usual care (the baseline period) was followed by a rollout period, during which the hospitals switched sequentially to the intervention (antibiotic prescription guided by the decision rule). At intervals of 4 weeks, hospitals were randomised to start the intervention between 28 August 2017 and 12 March 2018. This timing was chosen to take the seasonality of RTIs into account, as most eligible patients were expected during autumn and winter. Given the short duration of illness, the patients included in the different time periods were different people. The original and the final study protocol are available as S1 Text and S2 Text. The trial was approved by the ethics committee of Erasmus MC (MEC-2014-332) and by the participating hospitals. Written informed consent was obtained from the parents of all participants by the treating physician, in both phases of the trial. In the pre-intervention phase, this consent concerned the use of clinical data and performance of follow-up; in the intervention phase, it also concerned the use of the Feverkidstool to guide treatment decisions. Consent was obtained before calculating the predicted risk of the child. The trial was registered in the Netherlands Trial Register (NTR) (NTR5326). As reported in the NTR, 1 cluster was added during the pre-intervention period, to ensure sufficient inclusions. Interim analysis after the first year of data collection (but before implementation of the intervention) showed substantially higher antibiotic prescription rates than anticipated. Based on the distribution of risks and actual antibiotic prescription rates during the pre-intervention period, the target sample size was adjusted from 1,100 to 900 children, which is also reported in the NTR. No

other important methodological changes were made after the start of the trial. The study was reported according to the CONSORT guideline for clinical trials and the extension for stepped-wedge cluster randomised trials (S1 Table).

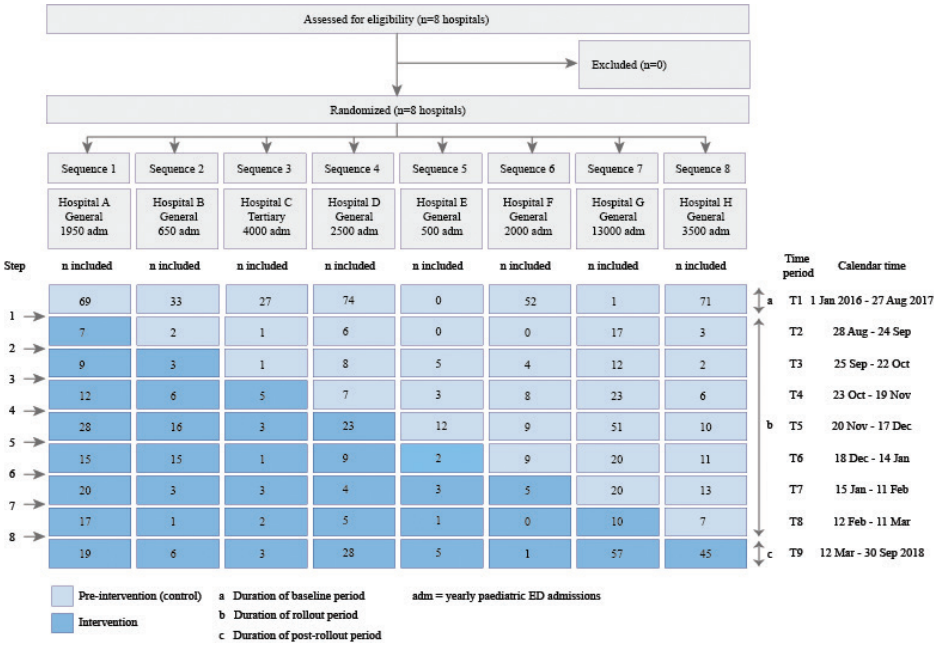

Fig 1. Design of the trial.

ED, emergency department.

Participants

We included children aged 1–60 months that presented with fever (reported by parents or measured as >38.5° C at the ED) and cough or dyspnoea as symptoms of potential lower RTI at the EDs of 8 hospitals in The Netherlands. This target population included children with all different risk profiles, since at presentation in the ED their risk profile was unknown. We excluded children at increased risk of a complicated course: children with relevant comorbidities, antibiotic use in the week prior to ED visit, amoxicillin allergies, another identifiable infectious focus (cutaneous, otitis media, tonsillitis), or signs of complicated pneumonia at presentation (oxygen saturation < 85%, respiratory insufficiency, empyema, sepsis). Relevant comorbidities were immunodeficiency, congenital heart defect, chronic pulmonary disease, multiple handicaps, and prematurity (born before the gestational age of 32 weeks and aged <1 year at time of presentation). Individual participants were included in the clusters by continuous recruitment by the treating physician in the ED. We included 8 hospitals in 6 cities of the southwest and central area of The Netherlands (a) where

paediatricians were responsible for the children presenting at the ED, (b) with varying ED sizes (range 500–13,000 annual paediatric ED admissions), (c) from diverse geographic and demographic regions (inner-city and mixed rural/urban), and (d) of different hospital types (tertiary and general). Hospitals were separated geographically, with no exchange of staff. The hospitals were recruited by the principal investigator (RO).

Randomisation and blinding

Randomisation of sequences of treatment was performed in July 2017 (after recruitment of all 8 clusters) by a statistician using computer randomisation. The statistician was involved as an advisor in the trial and was based at Erasmus MC. He knew the names of the other participating centres at randomisation, but had no further knowledge of these hospitals or relation to the local researchers. Since 2 hospitals started in August 2017 with the pre-intervention phase due to logistical reasons, these hospitals were randomised to start the intervention after time period 3 (Fig 1). This was accounted for in the original randomisation prior to the rollout period. The trial could not be blinded, because the intervention was the implementation and use of a decision rule by clinicians in the ED, including treatment advice based on the risk score that had to be calculated for each child.

Intervention

During the pre-intervention phase, all children received usual care. Usual care consisted of triage by a nurse, including the routine measurement of vital signs, followed by a clinical assessment and initiation of therapy by a physician, according to the Dutch and NICE guidelines for febrile children.[17,18] Additional diagnostics were performed at the discretion of the treating physician. CRP testing was often done as part of usual care, but without specific thresholds for decision-making. Other blood tests or chest X-rays were not routinely performed in children with suspected lower RTI, in line with the Dutch guideline, which is based on the British Thoracic Society guideline for the management of children with community-acquired pneumonia.[8] During usual care, antibiotics were prescribed at the discretion of the treating physician. Amoxicillin was usually prescribed as first-line treatment for community-acquired pneumonia.[8]

During the intervention phase, a validated clinical prediction model (Feverkidstool) was implemented as a decision rule guiding antibiotic prescription at the cluster level.[12,13] We predefined decision thresholds that would guide antibiotic treatment decisions, balancing positive and negative likelihood ratios and the consequences of over- and undertreatment.[12,19] The intervention was a decision-rule-based treatment strategy for all children with suspected lower RTI in the ED, with a differential effect on risk groups. In children with a low (≤3%) or

intermediate (4%–10%) predicted risk of bacterial pneumonia, antibiotics were withheld. In children with a high predicted risk (>10%), usual care was provided, i.e., antibiotics were prescribed at the discretion of the physician. The Feverkidstool included the following predictors: age in years, sex, duration of fever in days, ill appearance (yes/no), chest wall retractions (yes/no), capillary refill time in seconds, hypoxia (oxygen saturation < 94%), tachypnoea (based on Advanced Paediatric Life Support guideline), tachycardia (idem), temperature in degrees Celsius, and CRP in mg/l. Ill appearance was based on the judgment of the treating clinician. Although ill appearance was not defined by specific criteria, in the development and validation of the Feverkidstool this characteristic appeared to be valid and consistent among different populations.[12] More details about the development of the Feverkidstool have been published previously.[12] The tool was available to all treating physicians as an online digital calculator. The individual predicted risk was calculated after the physician's clinical assessment of the child and CRP testing, but before the treatment decision was made. During both phases of the study, a structured follow-up via telephone was performed 7 days after the ED visit. During the intervention phase, children with an intermediate or high predicted risk received an extra follow-up call 2 days after the ED visit to timely identify potential deterioration of the patient. When children were still hospitalised at those time points, the follow-up information was collected directly from the parents and the patient's electronic health record.

Outcomes

Primary outcomes were antibiotic prescription at ED discharge (yes/no) and strategy failure within 7 days after the initial ED visit (yes/no). Since the decision rule should not impact patient outcomes negatively (complying with our aim 'to safely reduce antibiotic prescriptions'), we viewed antibiotic prescription and strategy failure as equally important co-primary outcomes. Strategy failure was a composite outcome, based on the follow-up on day 7 and defined as secondary hospitalisation (i.e., hospitalisation during follow-up, after the initial discharge), secondary or switched antibiotic prescription (during follow-up), oxygen dependency or fever up to day 7, or the development of complications. Since there is no single and objective measure of failure of antibiotic treatment strategy, we used this predefined composite outcome for strategy failure. This outcome was chosen to cover different aspects of strategy failure that are important in clinical practice and may be related to the initial treatment strategy at the ED.[20] It includes changes in the treatment strategy for the child (secondary or switched antibiotic treatment and secondary hospitalisation) as well as signs of prolonged or complicated disease (oxygen dependency or fever up to day 7 and complications). Changes in treatment strategy during follow-up were made without specific recommendations in the study protocol. Reasons for switching antibiotic prescription

were not systematically recorded. Switching of antibiotics due to adverse drug reaction was considered a strategy failure. We used a short follow-up period of 1 week, assuming that a secondary hospitalisation within this time frame was related to the respiratory illness. All secondary prescriptions and secondary hospitalisations were considered a strategy failure. Secondary outcomes were the level of compliance to the intervention and the number of complications. Compliance was defined as the number of children in whom the Feverkidstool was calculated and who were treated according to the decision rule out of the total number of children included during the intervention phase. Complications were defined as the presence of pleural empyema, parapneumonic effusion (any size), pulmonary abscess, or respiratory insufficiency (need for mechanical ventilation) by day 7. No changes were made to the outcomes after the trial commenced.

Statistical methods

Sample size

We calculated the needed sample size for the 2 co-primary outcomes based on methods by Hussey and Hughes, without accounting for multiple testing.[16] We based our sample size calculation on the complete target population of children with suspected lower RTI in the ED, including all risk groups. Based on previous studies,[14] we assumed that 50% of the population would be at low risk, 30% at intermediate risk, and 20% at high risk, with antibiotic prescription rates of 35% (in the low-risk group), 40% (intermediate-risk group), and 85% (high-risk group). The decision rule was expected to affect risk groups differently: we estimated no difference in antibiotic prescription in the high-risk patients, and a reduction of 10–15 percentage points in the low-risk and intermediate-risk patients, leading to an overall reduction of antibiotic prescriptions of 10 percentage points. The intracluster correlation coefficient (ICC) was unknown, but we assumed a power of 90% at independency (i.e., no correlation between clusters, ICC of 0) would result in a power of 80% or more in multilevel analysis. We assumed different cluster sizes (small, intermediate, and large clusters) and 3-level seasonal variation in inclusion of patients. All assumptions are listed in S3 Text. Based on these assumptions, we originally estimated a needed sample size of 1,100 children with a suspected lower RTI. Interim analysis of inclusions during the first year showed a higher baseline prescription rate than was assumed. An interim power calculation based on this rate resulted in a needed sample size of 900 children to show superiority of the decision rule for antibiotic prescription with a power of 0.9 and an alpha of 0.05 (see S1 Text). This number was also sensitive to show non-inferiority of the intervention in terms of strategy failure with a non-inferiority margin of 5%: It could detect a 2-fold increase of secondary hospitalisation (the part of strategy failure with available baseline data: 5% at the time of original sample size calculation) with a power of 0.8 and alpha of 0.05. The interim

power analysis was performed before introduction of the intervention, so it was blinded to the outcomes of the trial.[21]

Primary analyses

We used multilevel generalised linear mixed models to calculate the impact of the intervention on our 2 primary outcomes: antibiotic prescription and strategy failure. Hospitals were added as a random effect to take clustering at the hospital level into account. Time period (1–9) was added as a fixed effect to adjust for a secular time trend introduced by the design of the study.[22] In the primary analyses we adjusted for pre-specified factors that may have influenced participation in the study or compliance to the protocol, i.e., age, sex, fever duration, season, and ill appearance. We tested the linearity of the associations between continuous predictors and outcomes. Detailed models can be found in the pre-specified statistical analysis plan (S4 Text). We performed an intention-to-treat analysis, i.e., the intervention population contained all of the children in the intervention phase, including those cases where doctors did not comply to the protocol (Fig 2). We analysed the outcome strategy failure in all children with follow-up information on strategy failure available. We also performed per-protocol analyses to evaluate the impact of the decision rule on the primary outcomes in cases of compliance to the protocol. For this per-protocol analysis, the intervention group consisted only of those children in whom the physicians complied to the protocol (Fig 2).

Secondary analyses

We report the level of compliance to the intervention and the number of complications during both phases of the study.

Pre-specified sensitivity analyses

We pre-specified 4 sensitivity analyses. First, to estimate the effect of the imputation of missing covariates on our primary analyses, we planned a sensitivity analysis on all covariates with >10% missing values, using different assumptions. Second, to evaluate the effect of loss to follow-up on the outcome strategy failure, we planned a sensitivity analysis assuming that (a) strategy failure occurred in all children with missing follow-up or (b) strategy failure occurred in none of those children. Third, to evaluate the effect of the longer baseline and post-rollout periods, we performed a sensitivity analysis of the primary outcome that only used data from 4 weeks before until 4 weeks after the rollout period (31 July 2017–8 April 2018), resulting in 9 time periods of equal length. Fourth, the level of routine measurement of CRP in the pre-intervention phase differed between hospitals. To adjust for this factor, we performed a sensitivity analysis on the data of only those hospitals that did perform routine CRP measurement in the population throughout both phases of the study.

Exploratory subgroup analysis. We performed an exploratory subgroup analysis of the primary outcomes in the different risk groups. Because our intervention was to withhold antibiotics in children at low or intermediate risk of bacterial pneumonia, we expected the most effect on primary outcomes in those risk groups. However, our study was not powered for subgroup analyses, so we performed these post hoc as exploratory analyses, to generate hypotheses for the interpretation of the overall primary results. We analysed the primary outcomes in the low- and intermediate-risk groups combined (≤10%) versus the high predicted risk (>10%) group, testing for a difference in effect using an interaction term (intervention × risk group). For these analyses we used the data of all children in whom the Feverkidstool—and thereby the risk group—could be calculated (complete case analysis), because we could not select subgroups based on imputed data. We did not perform other post hoc analyses.

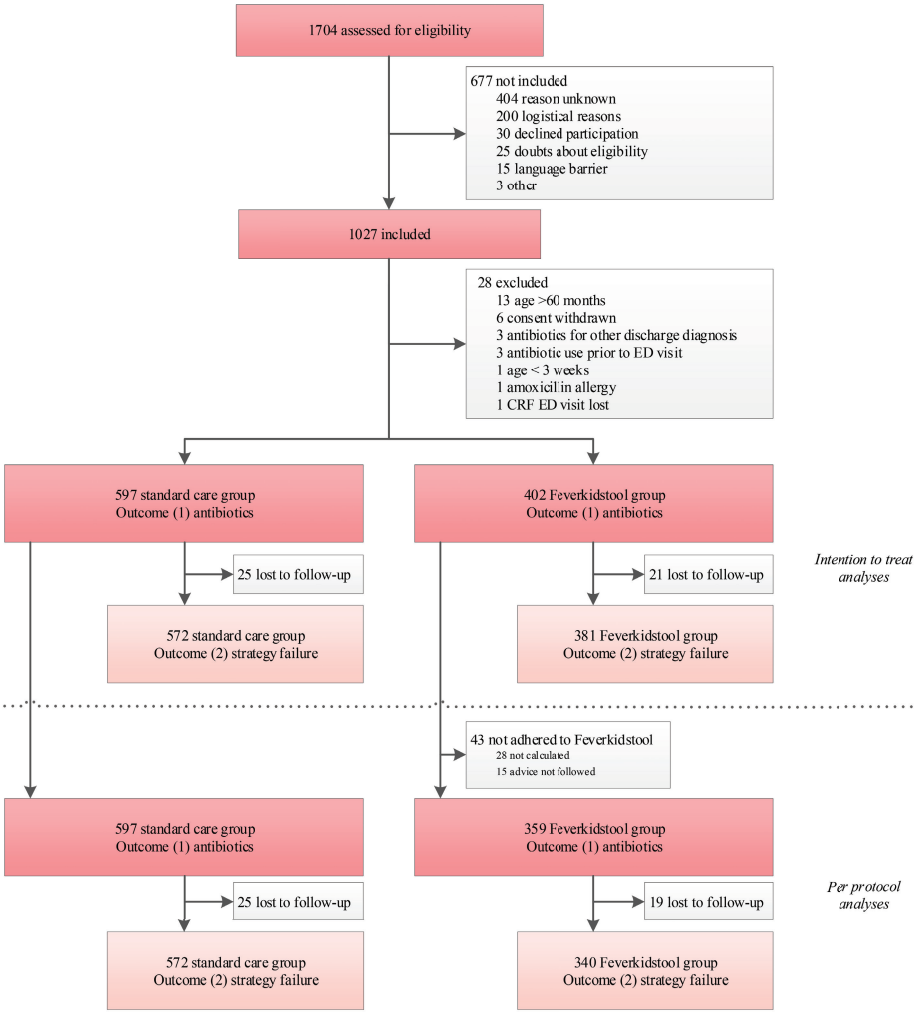

Fig 2. Flowchart of inclusion.
CRF, case report form; ED, emergency department.

Missing data

We assumed missing data to be missing at random, and handled missing covariates by means of multiple imputation using the mice package in R (version 3.3.4). The imputation model included all of the variables needed for the primary and sensitivity analyses, as well as additional information on diagnosis, treatment, disposition, and follow-up. Outcome variables (antibiotic prescription and strategy failure) were not imputed, except for the sensitivity analysis evaluating the effect of loss to follow-up on the outcome strategy failure. In this sensitivity analysis we used single imputation only for the outcome variable strategy failure,

assuming 100% failure if the variable was missing in one dataset versus 0% failure in another dataset. We did not impute predicted risk for the selection of risk groups in the exploratory analyses. If parents could not be reached for a follow-up on day 7 via telephone, follow-up information was retrieved from the child's electronic health record.

RESULTS

Recruitment

The baseline period ran from 1 January 2016 to 27 August 2017, and from 28 August 2017 to 12 March 2018 (the rollout period) the hospitals started the intervention phase one by one every 4 weeks; we collected data until 30 September 2018, when the target sample size was reached (Fig 1). All hospitals adhered to their allocated sequence of treatment and the planned rollout dates. All hospitals that were assessed for eligibility were recruited (n = 8); after recruitment, all 8 were randomised to a treatment sequence and included in the analyses (Fig 1). In total, 1,704 children were assessed for eligibility, and 1,027 children included in the trial (375 not included in the pre-intervention phase, 302 in the intervention phase). Of the included children, 28 children met the exclusion criteria, leaving 999 children for analyses of the primary outcome antibiotic prescription. Of these, 46 (5%) were lost to follow-up. Because the outcome strategy failure was based on follow-up, and because we did not impute outcome variables, the remaining 953 children were included in the analyses for strategy failure. Details of patient flow in the trial can be found in Fig 2, and details of inclusion at the cluster level in Fig 1. The main reason for non-inclusion of patients was that the ED was too busy to enrol patients in the trial. The children not included were generally less severely ill, reflected by a lower urgency at triage, fewer antibiotic prescriptions, and fewer hospitalisations (S2 Table).

Baseline data

The majority of children were male (n = 611, 61%), their median age was 17 months (interquartile range [IQR] 9 to 30), and most were referred to the ED by a general practitioner (Table 1). One-third of children appeared ill upon ED presentation, and the majority were tachycardic or tachypnoeic or exhibited chest wall retractions. Half of children were hospitalised, for a median duration of 3 days, mainly for oxygen therapy. During the pre-intervention phase, CRP testing was not routinely performed in all children, depending on differences in usual care in the participating hospitals. One hospital was a tertiary care centre; the others were general hospitals (see S3 Table for baseline characteristics per hospital). Annual admissions to the paediatric EDs ranged from 500 to 13,000 (Fig 1).

Table 1. Baseline characteristics of the study population.

Characteristic	Pre-intervention *n* = 597	Intervention *n* = 402
General characteristics		
Male sex	364/597 (61%)	246/402 (61%)
Age in months	17 (9–30)	17 (9–31)
Season		
Spring	76/597 (13%)	114/402 (28%)
Summer	55/597 (9%)	49/402 (12%)
Autumn	198/597 (33%)	88/402 (22%)
Winter	268/597 (45%)	151/402 (38%)
Way of referral to ED		
General practitioner	441/578 (76%)	295/379 (78%)
Self	66/578 (11%)	45/379 (12%)
Other healthcare professional	71/578 (12%)	39/379 (10%)
Triage level		
Immediate or very urgent	306/506 (60%)	182/332 (55%)
Urgent	146/506 (29%)	121/332 (36%)
Standard or non-urgent	54/506 (11%)	29/332 (9%)
Signs and symptoms		
Ill appearance*	220/572 (38%)	138/400 (35%)
Duration of fever in days	2 (1–4)	2 (1–4)
Temperature in °C	38.8 (38.1–39.5)	38.9 (38.1–39.5)
Hypoxia (oxygen saturation < 94%)	144/595 (24%)	74/401 (18%)
Tachycardia	416/595 (70%)	274/402 (68%)
Tachypnoea	487/581 (84%)	315/402 (78%)
Retractions	376/578 (65%)	237/401 (59%)
Dyspnoea	432/581 (74%)	290/402 (72%)
Wheezing	233/565 (41%)	132/395 (33%)
Prolonged capillary refill (≥2 seconds)	96/553 (17%)	19/401 (5%)
Management		
C-reactive protein test performed	372/597 (62%)	380/402 (95%)
C-reactive protein in mg/l	19 (7–44)	18 (7–38)
Chest X-ray performed	109/597 (18%)	49/402 (12%)
Discharge diagnosis		
Pneumonia	204/594 (34%)	110/401 (27%)
Bronchiolitis	117/594 (20%)	79/401 (20%)
Upper RTI	197/594 (33%)	156/401 (39%)
Viral induced wheeze	69/594 (12%)	49/401 (12%)
Other	7/594 (1%)	7/401 (2%)
Hospitalisation	329/597 (55%)	181/402 (45%)
Length of stay in days	3 (2–5)	3 (2–5)

Table 1. (continued)

Characteristic	Pre-intervention *n* = 597	Intervention *n* = 402
Reason for hospitalisation		
Oxygen therapy	235/329 (71%)	132/180 (73%)
Intake of antibiotics	8/329 (2%)	2/180 (1%)
Nebuliser bronchodilator	10/329 (3%)	4/180 (2%)
Monitoring	69/329 (21%)	39/180 (22%)
Other	7/329 (2%)	3/180 (2%)
Type of antibiotic prescribed		
Amoxicillin	152/179 (85%)	84/101 (83%)
Amoxicillin/clavulanic acid	8/179 (4%)	6/101 (6%)
Azithromycin	17/179 (9%)	4/101 (4%)
Cefuroxime	2/179 (1%)	1/101 (1%)
Other	0/179 (0%)	5/101 (5%)
Unknown	0/179 (0%)	1/101 (1%)

Footnote:

Categorical variables are presented as number/total (percentage), and continuous variables as median (interquartile range). The pre-intervention and intervention populations in a stepped-wedge trial cannot be directly compared, but should be adjusted for a secular time trend.[22]

**Based on physician's judgment (yes/no).*

ED, emergency department; RTI, respiratory tract infection.

Primary and sensitivity analyses

Overall antibiotic prescription was not reduced in the intervention phase (30% versus 25%; adjusted odds ratio [aOR] 1.07, 95% CI 0.57 to 2.01, p = 0.75; Table 2). Antibiotic prescription rates per hospital and per time period are provided in S4 Table. Strategy failure decreased from 23% in the pre-intervention phase to 16% in the intervention phase (aOR 0.53, 95% CI 0.32 to 0.88, p = 0.01). The per-protocol analysis gave similar results as the intention-to-treat analysis, showing that non-compliance to the decision rule did not influence the observed effect on the primary outcomes. Also the results of the sensitivity analysis with truncated baseline and post-rollout periods were comparable to the analyses on the whole population (Table 2). Two pre-planned sensitivity analyses were not needed: adjusting for missing covariates and adjusting for level of CRP measurement in pre-intervention phase. All covariates for the primary analyses had less than 10% missing values (Table 1), so we assume that no bias was introduced by multiple imputation. There was no difference in the level of CRP measurement between hospitals that performed CRP routinely during the pre-intervention phase and those that did not. Loss to follow-up had no effect on the outcome strategy failure, as shown by the sensitivity analyses that assumed different outcomes for those lost to follow-up (Table 2). Secondary antibiotic prescription was the most frequent reason for strategy failure (Table 2).

Table 2. Antibiotic prescription and strategy failure.

	Number/total (percentage)		Unadjusted		Adjusted	
Analysis and outcome	**Pre-intervention**	**Intervention**	**OR* (95% CI)**	***p*-Value†**	**OR‡ (95% CI)**	***p*-Value†**
Primary analyses						
Intention-to-treat population						
Antibiotic prescription	179/597 (30%)	101/402 (25%)	1.06 (0.61–1.85)	0.84	1.07 (0.57–2.01)	0.75
Strategy failure	131/572 (23%)	61/381 (16%)	**0.56 (0.34–0.93)**	**0.02**	**0.53 (0.32–0.88)**	**0.01**
Per-protocol population						
Antibiotic prescription	179/597 (30%)	83/359 (23%)	0.89 (0.5–1.61)	0.71	0.96 (0.49–1.88)	0.92
Strategy failure	131/572 (23%)	57/340 (17%)	**0.60 (0.36–1.00)**	**0.05**	**0.56 (0.34–0.93)**	**0.03**
Sensitivity analyses						
Truncated baseline and post-rollout periods§						
Antibiotic prescription	66/276 (24%)	64/279 (23%)	0.81 (0.45–1.46)	0.48	0.71 (0.38–1.32)	0.27
Strategy failure	58/261 (22%)	46/269 (17%)	**0.57 (0.35–0.94)**	**0.03**	**0.54 (0.33–0.90)**	**0.02**
Strategy failure, including missing values						
Assumption missing = failure	156/597 (26%)	82/402 (20%)	**0.56 (0.36–0.88)**	**0.01**	**0.55 (0.35–0.87)**	**0.01**
Assumption missing = no failure	131/597 (22%)	61/402 (15%)	**0.59 (0.36–0.96)**	**0.03**	**0.56 (0.34–0.91)**	**0.02**
Secondary analyses						
Compliance (Feverkidstool calculated and patient treated according to advice)	NA	359/402 (89%)				
Complications¶	1/572 (0.1%)	1/381 (0.2%)				
Strategy failure: reasons						
Secondary antibiotic prescription	45/572 (8%)	29/381 (8%)				
Changed antibiotics during follow-up	14/572 (2%)	5/381 (1%)				
Secondary hospitalisation**	16/572 (3%)	13/381 (3%)				
Oxygen need at day 7	9/572 (2%)	1/381 (0.2%)				
Fever at day 7	47/572 (8%)	13/381 (3%)				

Footnotes:
Bolding indicates statistical significance.
**Main model: clustered by hospital, adjusted for time period. Time-adjusted intracluster correlation coefficient for antibiotic prescription = 0.04, for strategy failure = 0.*
†p-Values based on multivariable logistic regression.
‡Adjusted model: main model further adjusted for age, sex, season, ill appearance, and duration of fever.
§Using data from 4 weeks before until 4 weeks after the rollout period, resulting in 9 time periods of equal length, truncating the prolonged baseline and post-rollout periods.
¶Complications were 1 admission to intensive care unit in the pre-intervention phase and 1 pleural empyema in the intervention phase (both unrelated to study intervention).
***Including 1 admission to the intensive care unit in the pre-intervention group.*
NA, not applicable.

Secondary analyses

In 43/402 (11%) cases, the clinician was not compliant with the decision rule (Table 2). Two complications occurred during the trial: in the pre-intervention phase 1 child was admitted to the intensive care unit during follow-up for mechanical ventilation; in the intervention phase 1 child developed pleural empyema at day 10. Both complications were unrelated to the study intervention, since both patients treated with antibiotics at the first ED visit.

Exploratory subgroup analysis: risk groups

We had complete information on all Feverkidstool predictors in 331/597 (55%) of the children in the pre-intervention phase. CRP was the most frequent missing variable (225/597, 38%). The complete case analysis showed that the effect of the decision rule was different across risk groups ($p < 0.01$; Table 3). Antibiotic prescription was lower in the low and intermediate risk groups combined (≤10% predicted risk) during the intervention phase, whereas in the high-risk group prescription rates were higher, but not statistically significantly so. The reduction in strategy failure was observed in the high-risk group (Table 3), mainly via fewer secondary antibiotic prescriptions and less frequent fever at day 7 (S5 Table).

Table 3. Exploratory subgroup analysis on complete cases (n = 705).*

	Number/total (percentage)		Unadjusted		Adjusted	
Subgroup analysis†	**Pre-intervention**	**Intervention**	**OR‡ (95% CI)**	***p*-Value§**	**OR¶ (95% CI)**	***p*-Value§**
Low/intermediate-risk population (<10%)						
Antibiotic prescription	29/172 (17%)	15/234 (6%)	**0.37 (0.15–0.94)**	**0.04**	**0.31 (0.12–0.81)**	**0.02**
Strategy failure	29/159 (18%)	39/218 (18%)	0.91 (0.43–1.90)	0.80	0.88 (0.42–1.87)	0.75
High-risk population (>10%)						
Antibiotic prescription	75/159 (47%)	83/140 (59%)	2.04 (0.84–4.94)	0.11	2.28 (0.84–6.17)	0.09
Strategy failure	42/155 (27%)	20/136 (15%)	0.45 (0.18–1.15)	0.10	**0.37 (0.14–0.99)**	**0.05**

Footnotes:

**331/597 (55%) cases were complete in the pre-intervention population, of which 172/331 (52%) were in the low or intermediate risk group (n = 91 low risk; n = 81 intermediate risk); 374/402 (93%) cases were complete in the intervention population, of which 234/374 (63%) were in the low or intermediate risk group (n = 115 low risk; n = 119 intermediate risk).*

†Interaction term intervention × risk group p < 0.01.

‡Main model: clustered by hospital, adjusted for time period.

§p-Values based on multivariable logistic regression.

¶Adjusted model: main model further adjusted for age, sex, season, ill appearance, and duration of fever.

DISCUSSION

We showed that a clinical decision rule did not reduce overall antibiotic prescription in children with suspected lower RTI in the ED, but that it did reduce strategy failure. Exploratory subgroup analyses showed that the intervention influenced the outcomes in the risk groups differently.

Our primary aim was to safely reduce antibiotic prescription in children under 5 years with suspected lower RTI at the ED. We hypothesized that introducing a decision rule as an intervention would safely reduce antibiotic prescriptions in these children. This target population included children with all different risk profiles, since at presentation in the ED their risk was unknown. The first primary endpoint of reducing antibiotic prescription was not met. The other primary endpoint of not increasing strategy failure was met. Moreover, we observed a reduction in strategy failure, suggesting that antibiotic prescriptions were more appropriately targeted to children who benefited from antibiotics. This additional hypothesis was supported by our exploratory subgroup analysis, showing a safe reduction in antibiotic treatments in the low/intermediate-risk group and a (non-significant) increase of prescriptions and a reduction of strategy failures in the high-risk children. This suggests a shift in antibiotic prescriptions from the low/intermediate-risk children towards the high-risk children who had more clinical benefit from the antibiotics. Our power calculation was based on the complete target population of children with suspected lower RTI, assuming a distribution of risk based on previous research. Post hoc sensitivity analysis of the sample size calculation showed that our study was sufficiently powered (power of 0.8), also when accounting for clustering at varying ICC values (range 0.01–0.26) and adjusted for multiple testing. However, we observed a smaller proportion of low/intermediate-risk children in our study population than expected. The shift in antibiotic prescriptions towards high-risk children and the observed smaller proportion of low/intermediate-risk children in our study may explain why we did not detect an overall reduction in antibiotic prescription. However, it must be noted that this finding was based on complete case analysis only and that our study was not powered for subgroup analyses.

We used a composite outcome to define strategy failure. Composite outcomes can be problematic, if the effect of the intervention is mainly driven by less important components.[20] In our study we found that a reduction in secondary antibiotic prescriptions was the main component of the reduction in strategy failures in the high-risk children and in those in whom we could not calculate the risk score (S5 Table). In low/intermediate-risk children, secondary prescription slightly increased, but without increasing oxygen need or fever at day 7 (proxies

for disease severity). There was no increase in complications during the intervention phase. These observations show that our intervention was safe, with reduced strategy failure on clinically important outcomes.

In this trial we used a threshold of 10% to define low/intermediate- versus high-risk patients, based on previous observed diagnostic performance,[12] which appeared to be safe. Given the relatively low observed antibiotic prescription rate in the high-risk group, a higher threshold may also be reasonable and more specific, but may carry a risk of increasing strategy failure. These considerations highlight the difficulty in obtaining the optimal balance between reducing overuse of antibiotics (important from a public health perspective) and at the same time striving for the best clinical outcomes for the individual patient.[19]

Other impact studies of decision rules for infections in children that combine biomarkers and clinical characteristics are scarce. In a previous impact study, the Feverkidstool was used as a decision rule to guide diagnostic decisions in febrile children in a tertiary hospital. This resulted in a more standardised diagnostic approach, but did not improve the study's secondary patient outcomes, namely antibiotic treatment and hospitalisation.[14] A study of Lab-score (a decision rule combining biomarkers) failed to prove its impact on antibiotic prescription in infants with fever without source.[23] Two studies have been reported in non-Western countries on the impact of decision rules on antibiotic prescription.[24,25] A bacterial pneumonia score reduced antibiotic prescription without increasing treatment failure,[24] but requires neutrophil testing and a chest X-ray, both of which are not recommended routinely for the management of children with suspected lower RTIs. In Tanzania an algorithm including clinical features, CRP, and procalcitonin (PCT) reduced antibiotic prescription from 94.9% to 11.5% and improved clinical outcomes in febrile children in primary care.[25] Most other studies focused on the impact of single point-of-care biomarkers on antibiotic prescription. A large study in Vietnam showed a reduction of antibiotic use after CRP testing for non-severe acute RTIs in adults as well as in children.[26] In the European ambulatory care setting, there is evidence that CRP testing can reduce immediate antibiotic prescription in children when appropriate guidance is provided to the healthcare professional.[27,28] A randomised controlled trial from Switzerland studied PCT-guided treatment, but found no effect on antibiotic prescription rates.[29]

To our knowledge, this is the first multicentre randomised trial designed to measure the impact of a clinical decision rule on antibiotic prescription in children with suspected lower RTI in the ED. A major strength is that our trial studied the impact of a decision rule on usual care. Because the trial was conducted in different settings, mostly general hospitals,

we believe our findings are generalisable to general paediatric practice. We had complete information on the outcome antibiotic prescription, good compliance to the protocol, a high follow-up rate, and sufficient power. The sensitivity analyses showed similar results as our primary analyses, confirming the robustness of our findings. There are also some limitations. Logistical problems in starting the trial in 2 hospitals resulted in a longer baseline period before rollout, potentially affecting the power of our study (Fig 1). However, the sensitivity analysis truncating this prolonged baseline period gave results similar to our main analysis, so we believe our overall estimates are valid. Another limitation is the amount of missing Feverkidstool variables in the pre-intervention phase, especially CRP. This did not influence our primary analyses (as CRP was not needed in these models), but limited the number of included patients in the subgroup analyses, where the calculated risk of the Feverkidstool was required. This may have introduced some bias in the subgroup analyses. Next, not all eligible children could be included in the trial. Doctors in the ED often are under time pressure, leaving insufficient time or attention to recruit patients for a trial, as has been acknowledged by other paediatric ED trials.[5,23] Comparison of the included and non-included children showed that severely ill children were included more frequently. This was the same in both phases of the study, and the rate of eligible children whose families declined participation was also stable over the study phases. Therefore, we believe there was no selection bias introduced by a lack of allocation concealment at the individual level. We believe that we did not miss any children with severe infections, so our results on strategy failure and complications are generalisable.

Although we could not prove an overall reduction of antibiotic prescription, our study implies that guiding antibiotic treatment by a decision rule based on the Feverkidstool is non-inferior in terms of safety in non-complex cases of suspected lower RTI. Moreover, patient outcomes may be improved by better targeting of antibiotics. Implementation of the decision rule in clinical practice would require measuring (point-of-care) CRP, which is not routinely done in all patients with fever and respiratory symptoms.[30] However, we recommend a low threshold for CRP measurements and risk assessments for bacterial pneumonia in these children, and withholding antibiotics in children with a predicted risk of ≤10%, provided that careful safety-netting and good access to healthcare are in place.[31] To avoid the risk of over-prescription in children with a predicted risk of >10%, this approach should be closely monitored. Future research should focus on the safety of higher decision thresholds and on the impact in settings with higher antibiotic prescription rates at baseline, or with a larger proportion of low-risk children. Our observed 30% antibiotic prescription rate at baseline for suspected lower RTIs is lower than what has been described in other European EDs, where antibiotic prescription rates range from 52% to 78%.[5,6,13,32] Even though the populations in

many studies cannot be directly compared, a recent paper showed that after adjustment for differences in population, large variability in antibiotic prescription remains.[1] We expect that the effect of our intervention on antibiotic prescription may therefore be larger in settings with a higher baseline prescription rate, or in populations with a larger proportion of low-risk children.

A clinical decision rule for childhood pneumonia did not reduce overall antibiotic prescription, but was non-inferior in terms of strategy failure. Exploratory analyses showed that the intervention reduced antibiotic prescriptions in low/intermediate-risk children, and that it reduced overall strategy failures, suggesting improved targeting of antibiotics by the decision rule.

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SUPPORTING INFORMATION

Available as online web appendix on website of PLOS Medicine:

- S1 Table. CONSORT checklist.
- S1 Text. Final approved trial protocol, version 7 (10 August 2018).
- S2 Text. Original approved trial protocol version 3 (03 April 2014).
- S4 Text. Pre-specified statistical analysis plan (14 December 2018).

S2 Table. Comparison of included and non-included children.

	Included n=999	Non-included n=677
General characteristics		
Male sex	610/999 (61%)	432/674 (64%)
Age in months*	17 (9 - 30)	12 (6 - 24)
Triage level*		
- *Immediate or very urgent*	488/908 (54%)	251/641 (39%)
- *Urgent*	267/908 (29%)	266/641 (41%)
- *Standard or non-urgent*	83/908 (9%)	124/641 (19%)
Antibiotic prescription*	280/999 (28%)	106/677 (16%)
Hospitalization*	510/999 (51%)	242/677 (36%)

* significant difference between included and non-included children, based on t-test for continuous outcomes and based on chi-squared test for categorical outcomes.

S3 Table. Baseline characteristics per hospital.

	Overall		**Hospital A**		**Hospital B**		**Hospital C**		**Hospital D**		**Hospital E**		**Hospital F**		**Hospital G**		**Hospital H**	
	n = 999		**n = 196**		**n = 85**		**n = 46**		**n = 164**		**n = 31**		**n = 98**		**n =211**		**n = 168**	
	n / median	%/IQR	*General hospital*		*General hospital*		*Tertiary hospital*		*General hospital*		*General hospital*		*General hospital*		*General hospital*		*General hospital*	
General characteristics																		
Male sex	611	61%	114	58%	58	68%	31	67%	97	59%	17	55%	54	55%	138	65%	101	60%
Age in months	17	9 - 30	13	8 - 25	18	10 - 33	22	11 - 37	15	8 - 30	19	12 - 27	14	9 - 26	20	10 - 34	16	9 - 28
Season																		
- *Spring*	190	19%	39	20%	16	19%	7	15%	29	18%	3	10%	16	16%	38	18%	42	25%
- *Summer*	104	10%	21	11%	4	5%	4	9%	16	10%	2	6%	9	9%	19	9%	29	17%
- *Autumn*	287	29%	43	22%	22	26%	18	39%	56	34%	12	39%	32	33%	70	33%	34	20%
- *Winter*	431	43%	93	47%	43	51%	17	37%	66	40%	14	45%	41	42%	84	40%	63	38%
Way of referral																		
- *General practitioner*	739	74%	148	76%	56	66%	19	41%	137	84%	18	58%	84	86%	136	64%	138	82%
- *Self*	111	11%	11	6%	4	5%	11	24%	8	5%	1	3%	3	3%	61	29%	12	7%
- *Other*	110	11%	30	15%	7	8%	11	24%	17	10%	12	39%	11	11%	13	6%	9	5%
Signs and symptoms																		
Ill appearance	359	36%	80	41%	25	29%	12	26%	89	54%	7	23%	37	38%	68	32%	40	24%
Duration of fever in days	2	1-4	2	1 - 4	3	1 - 4	3	1 - 5	2	1 - 3	2	1 - 4	2	1 - 4	2	1 - 3	2	1 - 3
Temperature	38.8	38.1 - 39.5	38.9	38.2 - 39.5	38.8	38.1 - 39.1	39.1	38 - 39.7	38.9	38.1 - 39.6	38.5	37.5 - 39.2	38.6	37.8 - 39.2	39.0	38.5 - 39.6	38.6	38 - 39.4
Hypoxia (sat <94%)	218	22%	36	18%	14	16%	10	22%	44	27%	3	10%	30	31%	56	27%	25	15%
Tachycardia	691	69%	124	63%	60	71%	32	70%	123	75%	23	74%	71	72%	133	63%	124	74%
Tachypnea	804	80%	140	71%	69	81%	35	76%	139	85%	18	58%	87	89%	169	80%	145	86%
Retractions present	614	61%	106	54%	57	67%	20	43%	114	70%	17	55%	59	60%	150	71%	90	54%
Dyspnea present	723	72%	133	68%	64	75%	27	59%	138	84%	21	68%	59	60%	161	76%	119	71%
Wheezing	366	37%	60	31%	31	36%	11	24%	69	42%	11	35%	21	21%	92	44%	70	42%
Prolonged capillary refill (≥2 seconds)	116	12%	21	11%	4	5%	4	9%	33	20%	0	0%	15	15%	31	15%	7	4%
Diagnostics and treatment																		
CRP performed	756	76%	136	69%	78	92%	39	85%	90	55%	27	87%	84	86%	137	65%	165	98%
CRP in mg/L	18	7 - 41	14	7 - 28	20	10 - 47	17	5 - 33	21	7 - 50	9	5 - 33	26	8 - 59	22	8 - 38	18	5 - 42
Chest x-ray performed	159	16%	17	9%	10	12%	6	13%	37	23%	14	45%	21	21%	37	18%	16	10%
Oxygen therapy	415	41%	65	33%	30	35%	14	30%	102	62%	9	29%	47	48%	80	38%	68	40%
Antibiotic prescription	281	28%	36	18%	17	20%	17	37%	65	40%	6	19%	37	38%	63	30%	39	23%
Hospitalization	511	51%	88	45%	39	46%	19	41%	119	73%	10	32%	58	59%	91	43%	86	51%

S4 Table. Antibiotic prescription per hospital and time period.

Time period	1	2	3	4	5	6	7	8	9
Hospital	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
A	11/69 (16%)	0/7 (0%)	2/9 (22%)	2/12 (17%)	5/28 (18%)	5/15 (33%)	4/20 (5%)	5/17 (29%)	2/19 (11%)
B	8/33 (24%)	0/2 (0%)	1/3 (33%)	0/6 (0%)	1/16 (6%)	2/15 (13%)	1/3 (33%)	1/1 (100%)	3/6 (50%)
C	10/27 (37%)	0/1 (0%)	1/1 (100%)	1/5 (20%)	0/3 (0%)	0/1 (0%)	2/3 (67%)	1/2 (50%)	2/3 (67%)
D	35/74 (47%)	3/6 (50%)	1/8 (13%)	3/7 (43%)	6/23 (26%)	3/9 (33%)	0/4 (0%)	3/5 (60%)	11/28 (39%)
E	0/0 (0%)	0/0 (0%)	1/5 (20%)	0/3 (0%)	3/12 (25%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	2/5 (40%)
F	23/52 (44%)	0/0 (0%)	1/4 (25%)	4/8 (50%)	0/9 (0%)	2/9 (22%)	2/5 (40%)	0/0 (0%)	5/11 (45%)
G	1/1 (100%)	3/17 (18%)	1/12 (8%)	5/23 (22%)	19/51 (37%)	6/20 (30%)	5/20 (25%)	5/10 (50%)	18/57 (32%)
H	27/71 (38%)	0/3 (0%)	0/2 (0%)	1/6 (17%)	1/10 (10%)	2/11 (18%)	1/13 (8%)	1/7 (14%)	6/45 (13%)

Footnote: dark grey = pre-intervention period; light grey = intervention period.

S5 Table. Detailed outcomes per risk group.

	Pre-intervention	Intervention
Low-intermediate risk population (≤10%)	**n / N (%)**	**n / N (%)**
Antibiotic prescription*	29/172 (17%)	15/234 (6%)
Strategy failure*	29/159 (18%)	39/218 (18%)
Strategy failure: reasons		
- *Secondary antibiotic prescription*	7/159 (4%)	20/218 (9%)
- *Changed antibiotics during follow-up*	1/159 (1%)	0/218 (0%)
- *Secondary hospitalization*	7/159 (4%)	11/218 (5%)
- *Oxygen need at day 7*	3/159 (2%)	0/218 (0%)
- *Fever at day 7*	11/159 (7%)	8/218 (4%)
High-risk population (>10%)		
Antibiotic prescription*	75/159 (47%)	83/140 (59%)
Strategy failure*	42/155 (27%)	20/136 (15%)
Strategy failure: reasons		
- *Secondary antibiotic prescription*	18/155 (12%)	8/136 (6%)
- *Changed antibiotics during follow-up*	6/155 (4%)	5/136 (4%)
- *Secondary hospitalization*	3/155 (2%)	2/136 (1%)
- *Oxygen need at day 7*	2/155 (1%)	1/136 (1%)
- *Fever at day 7*	13/155 (8%)	4/136 (3%)
Feverkidstool missing†		
Antibiotic prescription	75/266 (28%)	3/28 (11%)
Strategy failure	60/258 (23%)	2/27 (7%)

S5 Table. Detailed outcomes per risk group.

	Pre-intervention	Intervention
Strategy failure: reasons		
- Secondary antibiotic prescription	20/258 (8%)	1/27 (4%)
- Changed antibiotics during follow-up	7/258 (3%)	0/27 (0%)
- Secondary hospitalization	6/258 (2%)	0/27 (0%)
- Oxygen need at day 7	4/258 (2%)	0/27 (0%)
- Fever at day 7	23/258 (9%)	1/27 (4%)

Footnote:

** The pre-intervention and intervention populations in a stepped-wedge trial cannot be directly compared, but should be adjusted for a secular time-trend.[22]*

† In these children no risk could be calculated due to missing Feverkidstool variables, therefore these populations cannot be compared.

S3 Text. List of assumptions for power calculation.

Original power calculation:

- 6 hospitals, 6 time periods
- Distribution risk groups: 50% low-risk, 30% intermediate-risk, 20% high-risk
- Antibiotic prescription at baseline: 23% in low-risk children, 35% in intermediate-risk children, 85% in high-risk children
- Effect of intervention on antibiotic prescription: 10%-point reduction in low-risk children, 15%-point reduction in intermediate-risk children, no difference in high-risk children
- Varying cluster sizes: 2 small, 2 medium, 2 large hospitals
- Seasonality: baseline inclusion rate, 2 months 50% higher rate, 2 months 50% lower rate
- ICC is unknown, assume 90% power to be sufficient

Interim power calculation:

- 6 hospitals, 6 time periods
- Distribution risk groups: 50% low-risk, 30% intermediate-risk, 20% high-risk
- Antibiotic prescription at baseline: 35-45% in low-risk children, 40% in intermediate-risk children, 85% in high-risk children
- Effect of intervention on antibiotic prescription: 10%-point reduction in low-risk children, 15%-point reduction in intermediate-risk children, no difference in high-risk children
- Varying cluster sizes: 2 small, 2 medium, 2 large hospitals
- Seasonality: baseline inclusion rate, 2 months 50% higher rate, 2 months 50% lower rate
- ICC is unknown, assume 90% power to be sufficient

Chapter 3.3.

Cost study of a cluster randomized trial on a clinical decision rule guiding antibiotic treatment in children with suspected lower respiratory tract infections in the emergency department

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ABSTRACT

Background

Children with fever and respiratory symptoms represent a large patient group at the emergency department (ED). A decision rule-based treatment strategy improved targeting of antibiotics in these children in a recent clinical trial. This study aims to evaluate the impact of the decision rule on healthcare and societal costs, and to describe costs of children with suspected lower respiratory tract infections (RTIs) in the ED in general.

Methods

In a stepped-wedge, cluster randomized trial, we collected cost data of children aged 1 month to 5 years of age with fever and cough/dyspnea in 8 EDs in The Netherlands (2016–2018). We calculated medical costs and societal costs per patient, during usual care (n = 597), and when antibiotic prescription was guided by the decision rule (n = 402). We calculated cost-of-illness of this patient group and estimated their annual costs at national level.

Results

The cost-of-illness of children under 5 years with suspected lower RTIs in the ED was on average €2130 per patient. At population level this is €15 million per year in the Netherlands (€1.7 million/100,000 children under five). Mean costs per patient in usual care (€2300) were reduced to €1870 in the intervention phase (p=0.01). Main cost drivers were hospitalization and lost parental workdays.

Conclusions

Implementation of a decision rule-based treatment strategy in children with suspected lower RTI was cost-saving, due to a reduction in hospitalization and parental absenteeism. Given the high frequency of this disease in children, the decision rule has the potential to result in a considerable cost reduction at population level.

INTRODUCTION

Fever and respiratory symptoms are responsible for most pediatric visits to the emergency department (ED).[1] A substantial part of the children presenting with these complaints are suspected of a lower respiratory tract infection (RTI). Remarkably, little is known about the healthcare costs related to this patient group. Some studies have used information from national healthcare or claims databases to calculate the costs of children with infectious diseases or community-acquired pneumonia, but these sources do not provide detailed information on the actual cost of individual patients.[2,3] Other studies have focused more specifically on cost-effectiveness, for instance, of vaccine-preventable diseases,[4,5] or on the financial impact of hospitalization, only.[6,7] Uncomplicated lower RTIs do not often require complex or costly medical interventions. However, children with RTIs frequently need hospitalization and/or antibiotic treatment. Therefore, due to the large number of patients the total costs may become substantial. A minority of them require admission to the intensive care unit. As the child's illness may last for more than a week, at home recovery may be related to parental absenteeism at work, resulting in costs from a societal perspective.[8]

A recent stepped-wedge, cluster randomized trial showed that guiding antibiotic treatment by a clinical decision rule (based on prediction model Feverkidstool)[9] in children with suspected lower RTIs was safe.[10] It also reduced antibiotic prescriptions in children at low-intermediate risk of bacterial pneumonia and reduced overall strategy failures, suggesting improved targeting of antibiotics. In addition to its clinical benefits, its economic consequences need to be addressed. In this study detailed cost data were collected, providing specific information on the economic impact of the decision rule, but also providing information on the general cost-of-illness of this patient group. Insight in the main cost drivers can assist policy makers and clinicians, aiming to reduce health care costs.

This study aims to (1) evaluate the impact of the decision-rule based treatment strategy on health care and societal costs, and (2) describe the general cost-of-illness of children under five with suspected lower RTIs visiting the ED.

MATERIALS AND METHODS

Study design

This cost study was a pre-planned secondary analysis of the Study To Reduce Antibiotic prescription in childhood Pneumonia (STRAP, Netherlands Trial Register, NTR5326).[10] This stepped-wedge cluster randomized trial was performed in 8 EDs in The Netherlands between 2016 and 2018, to evaluate the impact of a decision rule-based treatment strategy (hereafter called 'decision rule') in children with suspected lower RTIs. The primary clinical outcomes were antibiotic prescription and strategy failure. In the current economic study, we performed (1) a cost study on the impact of the decision rule, and (2) a cost-of-illness analysis of children under five with suspected lower RTIs. Costs were calculated from both healthcare and societal perspectives.

Population and intervention

We included 999 children aged 1 month to 5 years who presented with fever and cough or dyspnoea at the ED. Those with complex co-morbidities, other identifiable infectious focus, prior treatment with antibiotics, complicated pneumonia or an allergy to amoxicillin were excluded. The study methods have been described in detail previously.[10] In summary, it consisted of 2 phases. In the pre-intervention phase, included patients (n = 597) received the usual care in any of the participating hospitals where they presented, according to the Dutch guideline for febrile children.[11] In the intervention phase, antibiotic prescription to the included children (n = 402) was guided by a decision rule. Antibiotic treatment was withheld in children with a low-intermediate predicted risk of pneumonia (<10%). Risk predictions were based on a validated clinical prediction model, the Feverkidstool, that combines clinical characteristics of a child and C-reactive protein (CRP).[9] The clinical characteristics included in the Feverkidstool are: age, sex, duration of fever, ill appearance, chest wall retractions, capillary refill time, hypoxia, tachypnoea, tachycardia and temperature. CRP was measured using a point-of-care test. The 2 co-primary clinical outcomes of the trial were antibiotic prescription at ED discharge and strategy failure, that was defined as secondary antibiotic prescriptions or hospitalisations, persistence of fever or oxygen dependency up to day 7, or complications.[10]

Data collection

Relevant information on all cost categories was captured on standardized case report forms (CRFs). During the ED visit, data were collected on referral, diagnostics, hospitalization and medication. Seven days later we performed telephone follow-up, collecting data on the duration of hospitalization, subsequent contacts with healthcare professionals after ED visit

and the number of days of parental absenteeism from a paid job. The responsible physicians in the participating hospitals completed the CRFs during the ED visit. Trained research staff carried out the follow-up contact and completed the appropriate CRF.

Cost calculations

We estimated the healthcare expenses by multiplying the volumes of consumed health care with the unit prices in euros (€). For the healthcare costs we calculated intramural and extramural costs. Extramural costs included costs of referral (by general practitioner or ambulance transportation) and eventual subsequent consultations with a general practitioner during the follow-up period. Intramural costs included costs for each healthcare provider (nurse, resident and pediatrician) at the ED per patient hour, costs of diagnostics and treatment, hospitalization and outpatient follow-up. Societal costs included the number of days of parental absenteeism from a paid job and their transportation costs.

The Dutch guideline for economic healthcare evaluations was used for the unit cost-prices of hours spent by healthcare providers, of diagnostics, of hospitalization and of transportation.[12] This guideline provides target prices for costs made by each category of healthcare provider, including taxes, social securities and yearly vacations. An estimation of the amount of time (in hours) healthcare providers spent per patient was based on a survey among the study hospitals. We obtained unit cost-price of pharmaceuticals from the Dutch Health Institute (Zorginstituut Nederland).[13] Productivity costs were calculated for parents or caregivers who could not attend their paid jobs. Costs were estimated by multiplying the average hourly cost of labour and the number of hours of absenteeism from paid jobs. Statistics Netherlands (CBS) provides target prices for each hour of absenteeism.[14]

Statistical analysis

We performed an intention-to-treat analysis for the cost of health care expenses and compared this between the groups of patients who received usual care (usual care group) and those who received the intervention (intervention group). Then we tested the cost differences at category level and the total cost difference between these groups. For this analysis we used t-tests with bootstrapping techniques to obtain 95% confidence intervals. For the calculation of the total cost difference (and 95% confidence interval) we assumed that missing cost data meant no costs, given the fact that missing data was mostly determined by only one cost category (societal costs). To test the influence of this assumption, we performed a sensitivity analysis using complete cases. For the cost-of-illness analysis of suspected lower RTIs we performed descriptive statistics, with data from all 999 patients. Analyses were performed in SPSS (version 25.0).

Generalization of costs to national level

For the extrapolation of the total costs to the national level, we multiplied the total costs per patient to the number of children with suspected lower RTIs at the ED in the Netherlands per year (our target population). Since we used trial data, this number is limited to children that meet the inclusion and exclusion criteria of the trial and of whom we had informed consent. To estimate the size of our target population, we first calculated the proportion of eligible children in the study hospitals. As denominator we used the total number of annual ED visits of children under five per hospital per year during the trial period. Then we multiplied this proportion by the total annual number of ED visits of children under five years in the Netherlands. This gave us the total estimated target population.[15,16]

RESULTS

Patient characteristics

The majority of the 999 included children were boys (61%). Their median age was 17 months. One-third had an ill appearance at presentation. The median duration of fever was 2 days at time of ED presentation. Pneumonia and upper RTI were the most frequent diagnoses (31% and 33%), followed by bronchiolitis (20%). The intervention did not significantly reduce overall antibiotic prescription (adjusted odds ratio 1.07, 95% CI 0.57–2.01). Strategy failure decreased from 23% in the pre-intervention period to 16% in the intervention period (adjusted odds ratio 0.53, 95% CI 0.32–0.88.[10] Detailed baseline characteristics and clinical outcomes of patients are shown in Table 1.

Table 1. Baseline characteristics of the population, n = 999

	Usual care	**Intervention**
	n = 597	**n = 402**
Male sex	364 (61%)	246 (61%)
Age in months	17 (9–30)	17 (9–31)
Ill appearance*	220 (38%)	138 (34%)
Duration of fever in days	2 (1–4)	2 (1–4)
Hypoxia (oxygen saturation <94%)	144 (24%)	74 (18%)
Dyspnea	432 (74%)	290 (72%)
C-reactive protein in mg/L	19 (7–44)	18 (7–38)
Working diagnosis**		
- Pneumonia	204 (34%)	110 (27%)
- Bronchiolitis	117 (20%)	79 (20%)
- Upper RTI	176 (30%)	149 (37%)
- Other	97 (16%)	63 (16%)

Table 1. (continued)

	Usual care n = 597	Intervention n = 402
Primary clinical outcomes		
- Antibiotic prescription at ED visit	179 (30%)	101 (25%)
- Therapy failure	131 (23%)	61 (16%)
Antibiotic prescription during follow-up	45 (8%)	29 (8%)

Footnotes:
All numbers are presented as n (%) or median (interquartile range)
RTI = respiratory tract infection; ED = emergency department
** clinical appearance as judged by the treating physician (ill/not ill).*
*** clinical diagnosis by the treating physician, based on all available information during the ED visit.*

Cost analysis of intervention based on the decision rule

The overall costs per patient decreased from €2296 to €1873 (–€423, 95% CI –€664 to –€141, p = 0.01, see Table 2). This is a reduction of 18% of total costs per patient. The sensitivity analysis of complete cases (n = 711) still showed a significant cost difference (–€352, 95% CI –€672 to –€39, p-value 0.03). Hospitalization decreased on average from 2.2 to 1.6 days per patient, accounting for a reduction of €366 per patient. As a second largest contributor, the decrease of parental absenteeism from paid job accounted for another €50 in cost-reduction per patient. Within the intramural costs only, the reduction was €367 per patient.

Table 2. Cost analysis decision rule

	Usual care		Intervention		
	n =	597	n =	402	Cost difference
Cost category	**Volume**	**Av. cost**	**Volume**	**Av. cost**	**(95% CI)**
Pre-hospital / referral	%		%		
Consultation of general practitioner	76%	€ 26	78%	€ 26	
Ambulance	4%	€ 28	3%	€ 21	
Outpatient department referral	5%	€ 5	4%	€ 4	
Self-referral or other	15%	€ 0	15%	€ 0	
Total pre-hospital/referral costs per patient		€ 58		€ 52	-€6 (-€20; €7)
Emergency department	Av. minutes		Av. minutes		
ED nurse	40	€ 28	40	€ 28	
Resident pediatrics	55	€ 40	60	€ 44	
Pediatrician	6	€ 13	6	€ 13	
Fixed costs (42%)		€ 34		€ 35	
Total ED costs per patient		€ 115		€ 120	€5 (€5; €5)*
Diagnostics	%		%		
CRP or CRP-POCT	63%	€ 3	95%	€ 5	
Blood diagnostics	25%	€ 1	21%	€ 1	
Chest X-ray	18%	€ 10	12%	€ 6	
PCR viruses	10%	€ 2	17%	€ 4	
Total diagnostics costs per patient		€ 16		€ 16	€0 (-€3; €2)
Hospitalization	Av. days		Av. days		
Length of stay	2.18	€ 1,398	1.65	€ 1,057	
Transfer to ICU (%)	0.2%	€ 1	0.00	€ 0	
Nursing days ICU	0.01	€ 24	0.00	€ 0	
Total hospitalization costs per patient		€ 1,423		€ 1,057	-€366 (-€591; -€148)
Medication	%		%		
Amoxicillin	38%	€ 4	32%	€ 4	
Salbutamol	52%	€ 2	44%	€ 1	
Total medication costs per patient		€ 6		€ 5	-€1 (-€2; €0)
Follow-up	%		%		
Recontact general practitioner	18%	€ 6	16%	€ 6	
Recontact outpatient department or ED	28%	€ 29	24%	€ 25	
Total follow-up costs per patient		€ 35		€ 31	-€4 (-€10; €2)
Societal costs	Av. no		Av. no		
Days of absenteeism (mother)	1.31	€ 330	1.23	€ 310	
Days of absenteeism (father)	1.01	€ 305	0.91	€ 275	
Round trip home-hospital	1.42	€ 4	1.36	€ 4	
Parking fees	1.42	€ 4	1.36	€ 4	
Total societal costs per patient		€ 643		€ 593	-€50 (-€148; €64)
Total costs per patient		**€ 2,296**		**€ 1,873**	-€423 (-€664; -€141)

Footnote:

ED = emergency department; CRP = C-reactive protein; POCT = point-of-care test; ICU = intensive care unit; Av = average.

**Confidence interval of zero, because there was no variability in costs at the individual level. There was a cost difference of €5 at category level because of extra time the resident needed in the intervention period to calculate the Feverkidstool, but this was the same for all children in that period.*

Cost-of-illness of suspected lower RTI

The general cost-of-illness of children under five with suspected lower RTI was €2126 per patient (see Table, Supplemental Digital Content 1). Costs of hospitalization accounted for 60% of these total costs. Each hospitalized patient cost €3433, whereas an outpatient cost €567. Societal costs, mainly those related to parental or caregiver absenteeism from a paid job accounted for one third of the total costs per patient, being the second largest cost driver. Diagnostics and medication contributed 1% to the total costs.

We observed considerable variation in the average cost per child between the various working diagnoses and age groups (see Table, Supplemental Digital Content 1). Patients with bronchiolitis cost €626 per outpatient and €4174 per hospitalized patient, being most expensive diagnosis. Bronchiolitis outpatients had highest societal costs (€412); bronchiolitis hospitalized patients had highest hospitalisation costs (€2946) and societal costs (€1023). Children with suspected pneumonia had highest costs of diagnostics and medication (€20 and €9). Outpatients in the age category 13-24 months had highest societal costs; in hospitalized patients this was in the age group <1 year.

Generalization costs to national level

Data on the total annual number of children <5 years visiting the ED during the study period was available in 7 of the 8 study locations. In those hospitals, 1095 patients under five with suspected lower RTI visited the ED per year, out of 20,040 ED visits of children under 5 in total (Table 3). Extrapolated to the national level, an estimated 7123 children with suspected lower RTI visit the EDs in The Netherlands each year. This resulted in a total annual cost of €15 million in the Dutch population, equivalent to €1.7 million per 100,000 children under five years old. If we also extrapolate the cost reduction of the decision rule (–18%) to the national level, the decision rule may save €2.7 million per year (€300,000/100,000 children under five per year).

Table 3. Estimation of annual costs at national level

Number of eligible patients in study hospitals per year	1095
Number of ED visits of children under 5 in study hospitals per year	20,040
Number of ED visits of children under 5 in The Netherlands per year	130,350
Number of children with suspected lower RTI in EDs in The Netherlands per year (target population)	7123
Total costs	**€ 15,034,145**

DISCUSSION

Main results

Health care costs of children under 5 with suspected lower RTIs visiting the EDs of participating hospitals were significantly lower for the decision rule-based treatment strategy than for usual care (€1870 vs. €2300). This cost reduction was mainly due to a reduced rate and duration of hospitalization. The main cost drivers in our study population were the number of days of hospitalization and parental or caregiver absenteeism from a paid job. Medication and diagnostic tests were most frequent in children with pneumonia, but had a low impact on the total costs. Children with bronchiolitis and younger ones were the most expensive category of patients, due to high hospitalization and societal costs. Extrapolating these estimations resulted in a total cost of €1.7 million per 100,000 children under 5 with suspected lower RTI in the ED per year; which is €15 million per year in The Netherlands; the decision rule may reduce 18% of these costs.

Interpretation of results and comparison to the literature

The observed reduction in costs in the intervention phase of the trial is in line with the observed clinical outcome of reduced strategy failure during the intervention. Strategy failure included among other things secondary hospitalization and oxygen need or fever at day 7. These factors reflect severity and duration of illness and are related to hospitalization and parental or caretaker absenteeism, the most important cost drivers. Even though the use of the decision rule required more frequent and more expensive CRP-measurements (due to use of a point-of-care test), and more time investment of the treating physician in the ED, these factors were negligible in terms of costs. Given the reduction of important cost drivers like hospitalization and absenteeism, the decision rule was cost-saving. Also the number of chest X-rays reduced, although these contributed little to the total costs.

To put our results in a more general perspective, we have included an overview of previous European cost-of-illness studies in Table 4. This includes reported costs, cost drivers and a comparison to our results. Most of these studies have focused on children with specific diagnoses. Two studies focused on children with community-acquired pneumonia (CAP): a Dutch and a Swiss study.[2,17] The Dutch CAP study reported similar health care costs per pediatric CAP patient as we found for children with a working diagnosis of pneumonia.[2] The Swiss study on CAP reported higher costs, especially for hospitalized patients. This difference may be due to differences in health care costs between Switzerland and The Netherlands and differences in the study populations, that is, older children in tertiary care, including more intensive care unit admissions.[17] Three studies reported on costs of children with bronchiolitis,

1 from Spain and 2 Dutch studies.[5,18,19] The Spanish study found comparable direct medical costs in the ED as we found in our study.[18] They also reported indirect or societal costs. However, unlike in our study, they focused only on the cost of ED visit and did not perform follow-up. Thereby they excluded costs of hospitalization and absenteeism during follow-up, the main cost drivers in our study. The two Dutch bronchiolitis studies focused on hospitalized children only.[5,19] One reported lower intramural and societal costs than we observed.[5] The second, on the other hand, found comparable costs for hospitalization.[19] One study from Germany studied a population of children under three years old with lower RTIs, and found comparable health care costs for hospitalized patients.[8] The costs of their outpatients were lower than ours. This may be explained by the fact that their patients were recruited from office-based pediatric practices instead of hospital-based EDs. Their reported number of days of parental absenteeism (0.5–1.5 days) was similar to that in our study.

In line with our results, all studies reported major cost drivers to be hospitalization or length of hospitalization, severity of disease, young age and societal costs. Overall, our results support those of previous studies that focused on specific diagnoses. However, we are the first to report the health care costs of a broader population of non-complex children under 5 presenting at the ED with fever and respiratory complaints. Though costs per patient may not seem extremely high, due to the high burden of these illnesses in children the total costs for hospitals and society may still be quite substantial. These findings may easily be extrapolated to other comparable settings in the EU, since respiratory infections are the most common reason of fever in pediatric EDs in most countries.[20] However, one should be cautious in generalizing our specific cost data to other settings as the exact unit costs per patient might differ in other countries due to differences in epidemiology, health care system, guidelines and organization of pediatric care.[21]

Table 4. Comparison cost-of-illness to the literature

Study, year (country)(ref)	Population: diagnosis, age, setting, study period (n)	Reported costs in €	Reported main cost drivers	Cost comparison STRAP in €*
Rozenbaum, 2015 (Netherlands)[2]	CAP, 0-9 years, national claims database, 2008-2011 (n=16809 inpatient; n=17727 outpatient)	Inpatient medical costs: 2548 Outpatient medical costs: 482	Hospitalization (93% of medical costs)	*0-5y, diagnosis pneumonia* Inpatient medical costs (n=196): 2421 Outpatient medical costs (n=118): 214
Keitel, 2014 (Switzerland)[17]	CAP, 2 months - 16 years, tertiary centre, 2008-2010 (n=174 total; n=96 outpatient; n=78 inpatient, of whom n=12 ICU)	Inpatient total costs: 21996 Outpatient total costs: 929 Societal overall costs: 146	Severe pneumonia (ICU admission, surgical procedures)	*0-5y, diagnosis pneumonia* Inpatient total costs (n=196): 3220 Outpatient total costs (n=118): 551 Overall societal costs (n=314): 624
Garcia-Marcos, 2014 (Spain)[18]	Bronchiolitis (first episode of respiratory distress and wheezing, preceded by common cold), <2 years, ED, 2010-2011 (n=664)	ED total costs: 250 ED medical costs: 213 ED societal costs: 35	RSV test positive, severe disease	*0-2y, diagnosis bronchiolitis* ED medical costs (n=174): 130
Miedema, 2011 (Netherlands)[5]	Bronchiolitis, median age 79 days (range 9-537d), hospitalized, 1998-2000 (n=73)	Inpatient total costs: 1964 Inpatient medical costs: 1702 Inpatient societal costs: 262	Hospitalization, societal costs	*0-2y, diagnosis bronchiolitis, hospitalized* Inpatient total costs (n=131): 4302 Inpatient medical costs (n=131): 3367 Inpatient societal costs (n=131): 1067
Rietveld, 2004 (Netherlands)[19]	Hospitalized for RSV, <1 year of age at start RSV season, different hospital types, 1996-2000 (n=3458)	Inpatient medical costs: 3110	Young age, length of stay, BPD, hospital type	*0-1y, diagnosis bronchiolitis, hospitalized* Inpatient medical costs (n=104): 3446
Ehlken, 2005 (Germany)[8]	Lower RTI, 0-3 years, office-based paedatric practice and hospitals, 1999-2001 (n=2039 inpatient; n=1329 outpatient)	Inpatient total costs: 2579 Outpatient total costs: 123	Hospitalization (95% of medical costs)	*0-3y, diagnosis pneumonia* Inpatient total costs (n=137): 3218 Outpatient total costs (n=86): 547 *0-3y, diagnosis bronchiolitis* Inpatient total costs (n=135): 4180 Outpatient total costs (n=48): 625

*Footnote: *STRAP estimates show the computed costs using the STRAP trial data but adjusted to the population of the publications it is compared to.*
RSV = respiratory syncytial virus; BPD = bronchopulmonary dysplasia; STRAP = Study to reduce antibiotic prescription in childhood pneumonia; ICU = intensive care unit

Strengths and limitations

The main strength of this study is the availability of prospectively collected, quality cost data of each participating patient, including health care and societal costs. The availability of data from a diversity of patients from both secondary and one tertiary hospitals in the Netherlands makes our study population a representable sample from the target population of non-complex children with suspected lower RTIs in the Netherlands. This makes it easy for our results to be reliably extrapolated to the national levels. There were also a number of limitations. Because of our strict inclusion and exclusion criteria, our results may not be generalizable to the children with co-morbidities, complicated illness or prior antibiotic treatment. It is plausible to assume that disease severity and subsequent health care costs in these groups will be higher than in our study population. We had missing data on parental of caregiver absenteeism in up to 20% of cases. This may have introduced some unexpected bias to our results.

Implications for clinical practice, policy and research

Our detailed cost data can assist not only policymakers in health care, but also clinicians and researchers. In addition to the clinical benefits of the decision rule, we have now proven that the rule is cost-saving in an ED population of 8 hospitals in The Netherlands. At national level this may result in a cost reduction of €2.7 million (or €300,000/100,000 children under five) per year. Since our cost estimates are in line with other European studies, we expect that the decision rule may result in a general cost reduction when implemented in other settings. CRP-measurements for calculating the Feverkidstool hardly impacted the total costs. This should not be a barrier for clinicians using the decision rule. Efforts to reduce rates and duration of hospitalization may achieve the largest cost reduction in pediatric emergency care. The large variability in hospitalization supports that there is room for improvement in hospitals and countries with a high rate and duration of admission.[22,23] However, less admissions and early discharge may result in an increase in costs related to parental or caregiver absenteeism, particularly in situations where children are not yet fully recovered at discharge. Increasing certainty of diagnosis by implementing new diagnostic tools may also reduce the need for additional testing, precautionary treatment or hospitalization.[24] However, interventions focusing on improving the outcome of children with RTIs (hospitalization or antibiotic prescription) may have larger impact on costs than interventions focusing on the diagnostics.[25] Lastly, we observed highest costs for children with bronchiolitis, even in our study population that excluded complex co-morbidities. So, preventive strategies for the most common (viral) pathogens of bronchiolitis implemented at a larger scale may have high cost-saving potential.[26]

Conclusion

The implementation of a decision rule-based treatment strategy in children with suspected lower RTI at the ED was cost-saving in The Netherlands. Major cost drivers in this patient group are young age, severity of disease, duration of hospitalization and societal costs. The cost reduction by the decision rule was mainly caused by less hospitalization and less parental absenteeism from a paid job. Given the high frequency of suspected lower RTIs in children, the decision rule may result in a considerable cost reduction if implemented at national or international level.

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Supplementary files

Supplementary digital content 1. Cost-of-illness of suspected lower RTIs in the ED

	n	Referral	ED	Diagnostics	Hospitalization	Medication	Follow-up	Societal	Total costs
Overall (all patients)	999	€ 56	€ 117	€ 16	€ 1.275	€ 5	€ 33	€ 624	**€ 2.126**
Outpatients	454	€ 57	€ 117	€ 11	€ 0	€ 4	€ 38	€ 341	**€ 567**
Working diagnosis									
Pneumonia	118 (26%)	€ 35	€ 117	€ 20	€ 0	€ 9	€ 33	€ 338	€ 551
Bronchiolitis	48 (11%)	€ 46	€ 117	€ 9	€ 0	€ 3	€ 39	€ 412	€ 626
Upper RTI	215 (47%)	€ 72	€ 117	€ 8	€ 0	€ 2	€ 44	€ 329	€ 572
Other	71 (16%)	€ 56	€ 117	€ 6	€ 0	€ 3	€ 27	€ 312	€ 521
Age groups									
1-12 months	145 (32%)	€ 38	€ 117	€ 9	€ 0	€ 3	€ 41	€ 371	€ 578
13-24 months	151 (33%)	€ 56	€ 117	€ 11	€ 0	€ 5	€ 41	€ 387	€ 617
15-59 months	158 (35%)	€ 76	€ 117	€ 13	€ 0	€ 5	€ 33	€ 264	€ 508
Hospitalized patients	545	€ 55	€ 117	€ 20	€ 2.351	€ 6	€ 29	€ 855	**€ 3.433**
Working diagnosis									
Pneumonia	196 (36%)	€ 51	€ 116	€ 32	€ 2.184	€ 10	€ 28	€ 799	€ 3.220
Bronchiolitis	148 (27%)	€ 40	€ 117	€ 15	€ 2.946	€ 5	€ 29	€ 1.023	€ 4.174
Upper RTI	110 (20%)	€ 80	€ 117	€ 14	€ 2.106	€ 5	€ 40	€ 851	€ 3.211
Other	89 (16%)	€ 58	€ 117	€ 11	€ 2.019	€ 4	€ 22	€ 710	€ 2.939
Age groups									
1-12 months	202 (37%)	€ 50	€ 117	€ 16	€ 2.724	€ 5	€ 33	€ 1.028	€ 3.972
13-24 months	144 (26%)	€ 57	€ 117	€ 17	€ 2.123	€ 6	€ 33	€ 723	€ 3.076
15-59 months	199 (37%)	€ 58	€ 116	€ 27	€ 2.137	€ 8	€ 22	€ 769	€ 3.137

Footnote: ED = emergency department; RTI= respiratory tract infection.

Chapter 3.4.

Update of a clinical prediction model for serious bacterial infections in preschool children by adding a host-protein based assay: a diagnostic study

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ABSTRACT

Objective

To determine whether updating a diagnostic prediction model by adding a combination assay (tumour necrosis factor-related apoptosis-inducing ligand, interferon γ induced protein-10 and C reactive protein (CRP)) can accurately identify children with pneumonia or other serious bacterial infections (SBIs).

Design

Observational double-blind diagnostic study.

Setting

Two hospitals in Israel and four hospitals in the Netherlands.

Patients

591 children, aged 1–60 months, presenting with lower respiratory tract infections or fever without source. 96 of them had SBIs. The original Feverkidstool, a polytomous logistic regression model including clinical variables and CRP, was recalibrated and thereafter updated by using the assay.

Main outcome measures

Pneumonia, other SBIs or no SBI.

Results

The recalibrated original Feverkidstool discriminated well between SBI and viral infections, with a c-statistic for pneumonia of 0.84 (95% CI 0.77 to 0.92) and 0.82 (95% CI 0.77 to 0.86) for other SBIs. The discriminatory ability increased when CRP was replaced by the combination assay; c-statistic for pneumonia increased to 0.89 (95% CI 0.82 to 0.96) and for other SBI to 0.91 (95% CI 0.87 to 0.94). This updated Feverkidstool improved diagnosis of SBIs mainly in children with low-moderate risk estimates of SBIs.

Conclusion

We improved the diagnostic accuracy of the Feverkidstool by replacing CRP with a combination assay to predict pneumonia or other SBIs in febrile children. The updated Feverkidstool has the largest potential to rule out bacterial infections and thus to decrease unnecessary antibiotic prescription in children with low-to-moderate predicted risk of SBIs.

INTRODUCTION

Suspicion of infectious disease is one of the most common cause of paediatric emergency department (ED) visits.[1] The proportion of bacterial infections in children with fever without source (FWS) and acute respiratory tract infections (RTI) is however low (respectively 0.02–13% and 26–28%).[2-4] Next, identifying patients benefiting from antibiotic treatment remains a major diagnostic challenge. Consequentially, children with acute RTI receive antibiotics almost twice as often as the estimated prevalence.[2,5,6] Antibiotic overuse is associated with increased antibiotic resistance, causing 25,000 deaths in Europe annually.[7,8] This underlines the need to better differentiate between viral and bacterial infections. Therefore, several prediction models have been developed.[9,10] The Feverkidstool, a clinical prediction model including both clinical parameters and C reactive protein (CRP), is a validated tool for supporting clinical decision-making on, for example, whether or not to start antibiotics.[11-13] However, further improvement of this diagnostic tool is warranted as it does not provide an accurate diagnosis for all patients.

We recently showed that a novel blood assay, combining concentrations of CRP with tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and interferon γ induced protein-10 (IP-10), could diagnose bacterial infections more accurate than CRP alone.[14-16]

The dynamics of TRAIL are complementary to traditionally studied bacteria-induced proteins; TRAIL concentrations decrease in bacterial infection and increase in viral infections.[15] The aim of this study is to investigate whether updating the Feverkidstool by replacing CRP with the combination assay can improve the diagnosis of SBI in preschool children.

PATIENTS AND METHODS

The current study builds on the prospective observational OPPORTUNITY Study performed in four hospitals in the Netherlands and two hospitals in Israel between 16 October 2013 and 28 January 2015. For detailed methods, we refer to the original publication.[14] In short, this study included clinical data, a host-protein based assay, nasal swab PCR and 28-day follow-up data from children aged 1–60 months with lower RTI or FWS (n=777). The study was an observational double-blind diagnostic study. The analysis of the serum samples for the assay (index test) was done in the absence of any clinical or other patient-related information, and the expert panel (reference standard) was blinded to the decisions of their peers and to the results of the index test.

General inclusion and exclusion criteria can be found in the original publication that had 577 children in the primary analysis. We added to our current study data of children aged 1–2

months that in the original OPPORTUNITY Study were included for a subanalysis (n=28), as this study showed accurate results of the assay in this population. Children admitted to the intensive care (all referred from the wards of other hospitals, n=14) were excluded as the Feverkidstool was developed for febrile patients presenting at the ED (online supplementary figure 1). Patients gave written informed consent prior to sampling. This study was designed and analysed without patient involvement. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. This manuscript follows the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) (online supplementary file 3) reporting guidelines.

Prediction model

The Feverkidstool is a polytomous prediction model that predicts the risk of pneumonia or other SBIs, based on the following variables: age, body temperature, heart rate, respiratory rate, oxygen saturation, ill-appearance, peripheral capillary refill, chest wall retractions and CRP (definitions presented in the statistical analysis plan, online supplementary file 1).[12]

Combined host-protein based assay

The assay is currently ELISA based (a point-of-care test is being developed) and combines the concentrations of TRAIL, IP-10 and CRP using a predetermined logistic regression formula to compute the likelihood score for a bacterial infection.[14,15] The assay was performed on coded serum samples in absence of any patient-related information.

Reference standard diagnosis

Currently, no single reference standard test exists for determining the aetiology of an infection.[17] Therefore, in the OPPORTUNITY Study, England's National Health Service's standard for evaluating diagnostic tests was followed and an expert panel reference standard was composed.[14,18] Every recruited patient was diagnosed by three panel members affiliated to the country of recruitment using all available electronic Case Record Form (eCRF) information (clinical and laboratory information, including a 28-day follow-up), but blinded to the assay and Feverkidstool results and to the labels of their peers. Each expert assigned one of the following aetiologies to each patient: bacterial infection, viral infection, mixed infection (ie, bacterial and viral co-infection), non-infectious disease or indeterminate. Patients assigned as mixed infection were later classified as bacterial because they are clinically managed similarly. Patients with a bacterial reference standard diagnosis were divided into pneumonia or other SBIs (e.g. meningitis, urinary tract infections, bacteraemia) based on the diagnosis at hospital discharge assigned by the attending physician.

Statistical analysis

General approach

We compared the diagnostic accuracy to predict SBIs of the original Feverkidstool with the accuracy of the Feverkidstool updated with the assay (hereafter called updated Feverkidstool). Statistical analyses were performed in SPSS version 21.0 for Windows and R V.3.2.2. We used the Mann-Whitney U test for comparison of continuous variables. Categorical outcomes were analysed using the χ^2 test or Fisher's exact test where expected cell counts were less than 5.

Model development and performance

First, we recalibrated the original Feverkidstool on our data using two separate logistic regressions, one for pneumonia and one for other SBIs (recalibrated Feverkidstool: *logit (pneumonia or other SBI)*= $\beta_0 + \beta_1$ (linear predictor Feverkidstool)). Then, we updated the Feverkidstool by adding the combination assay (updated Feverkidstool: *logit (pneumonia or other SBI)*= $\beta_0 + \beta_{2a}$ (linear predictor Feverkidstool) + β_{2b} (score assay)). One element of the assay, CRP, was also a predictor in the linear predictor Feverkidstool. To be able to compare the effect of using the assay (updated Feverkidstool) instead of the CRP only (original Feverkidstool) we standardised the effect of the CRP coefficient (as part of the linear predictor Feverkidstool) in this updated Feverkidstool. Therefore the linear predictor Feverkidstool was based on the median CRP value for all participants. The actual CRP value of patients was used to compute the score assay. Detailed models are presented in the statistical analysis plan (online supplementary file 1). The discriminative ability of the recalibrated original and updated models was expressed using pairwise c-statistics.[19]

Predicted risk thresholds

To help interpret the potential benefit of the different models along the range of predicted probabilities, a decision curve analysis (DCA) was performed. The DCA assesses the relative harm of false positives and false negatives for different probability thresholds if the models were used to guide antibiotic prescription.[20] For predefined risk thresholds, we calculated sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio (LR+, LR-) for the original and updated models.

Reclassification

To assess the potential added value of the updated Feverkidstool in correctly classifying SBIs and viral infections using defined thresholds, we did a head-to-head comparison for the updated Feverkidstool and the recalibrated original Feverkidstool in a reclassification table.[21]

Missing values

Multiple imputation techniques enabled analysing all available data. Missing values in the variables, needed for the Feverkidstool, were imputed 10 times using the multivariate imputation by chained equations (MICE) algorithm in R statistical software.[22] Variables used in the imputation model are presented in the statistical analyses plan (online supplementary file 1). Analyses were performed separately in the 10 imputed data sets and combined using Rubin's rules.[23] The Feverkidstool variable peripheral capillary refill was not recorded in the OPPORTUNITY Study for any patient. Because we had no information on the distribution of values for capillary refill, we could not include this variable in the model for multiple imputation. Leaving the coefficient for capillary refill out of the Feverkidstool would have led to systematic lower predictions (biased calibration), so we replaced this systematic missing variable by the mean prevalence of the prolonged capillary refill in the initial Feverkidstool derivation cohort (=0.039, mean imputation).[24] Inconclusive diagnoses (n=71) were also imputed; a sensitivity analysis was performed leaving out patients with an inconclusive diagnosis.

RESULTS

Population characteristics

A total of 591 patients were available for analysis: 30 pneumonia, 66 other SBIs and 495 viral infections (online supplementary figure 1). Children with pneumonia were older than children with other SBIs or with viral infections (median age of 24.5 versus 15 months) and children with pneumonia or other SBIs were hospitalised more often (73% and 77%) than children with viral infections (52%, table 1). Children with an inconclusive reference standard diagnosis differed from children with a conclusive diagnosis on age, biomarker values and antibiotic prescription (online supplementary table 1).

Table 1. Characteristics of patients included in the primary analysis

	Pneumonia (n=30)	**Other SBI (n=66)**	**Viral (n=495)**
Predictor variables			
Age (months)	24.5 (12.7–41.3)	15.0 (8.0–33.0)	15.0 (7.0–28.0)
Gender, male	19 (63%)	32 (49%)	280 (57%)
Duration of fever (days)	3 (2-5)	2 (1-4)	2 (1–4)
Temperature (°C)	38.6 (38.2–39.8)	38.7(37.8–39.4)	38.5 (37.6–39.2)
	n=30 (100%)	n=66 (100%)	n=493 (99%)
Respiratory rate	50 (34-70)	40 (31–52)	38 (30-52)
	n=15 (50%)	n=31 (47%)	n=252 (51%)
Tachypnea	12 (80%)	17 (55%)	130 (52%)

Table 1. (continued)

	Pneumonia (n=30)	Other SBI (n=66)	Viral (n=495)
Heart rate	160 (24)	152 (27)	151 (24)
	n=29 (97%)	n=57 (86%)	n=453 (92%)
Tachycardia	21 (72%)	29 (51%)	232 (51%)
Oxygen saturation (%O_2)	98 (97-99)	99 (97–100)	98 (96–100)
	n=28 (93%)	n=48 (73%)	n=417 (84%)
Desaturation (<94%O_2)	1 (4%)	0 (0%)	24 (6%)
Chest wall retractions	6 (20%)	4 (6%)	60 (12%)
	n=30 (100%)	n=63 (95%)	n=484 (98%)
Ill appearance	13 (43%)	25 (38%)	141 (29%)
C-reactive protein (mg/l)	176 (72–224)	102 (55–151)	15 (5–36)
Assay score	98 (76–100)	88 (68–98)	4 (1–26)
Other variables			
Hospital admission	22 (73%)	51 (77%)	255 (52%)
Hospitalization duration (days)	4 (3–6)	4 (3–5)	3 (2–4)
Antibiotic treatment prescribed	30 (100%)	63 (96%)	140 (29%)
Recruiting site			
Secondary care centre	27 (90%)	63 (96%)	463 (94%)
Tertiary care centre	3 (10%)	3 (4%)	32 (6%)
Focus of infection			
Central nervous system	0 (0%)	0 (0%)	9 (2%)
Gastrointestinal tract	0 (0%)	1 (2%)	19 (4%)
Other	3 (10%)	11 (17%)	39 (8%)
Respiratory tract	26 (87%)	18 (27%)	250 (50%)
Systemic	0 (0%)	2 (3%)	9 (2%)
Unknown	1 (3%)	10 (15%)	169 (34%)
Urinary tract	0 (0%)	24 (36%)	0 (0%)

Data are presented as n (%), median (IQR) or mean (SD). This table includes imputed reference standard diagnoses, data are based on 1 of the 10 imputed datasets. If data were not available for all patients, the total number of available data are noted. Clinical syndrome was based on the diagnosis of the attending physician at discharge from the hospital. LRTI included pneumonia and bronchiolitis; URTI included laryngitis, pharyngitis, otitis media, sinusitis and tonsillitis. SBI, serious bacterial infection.

Model performance

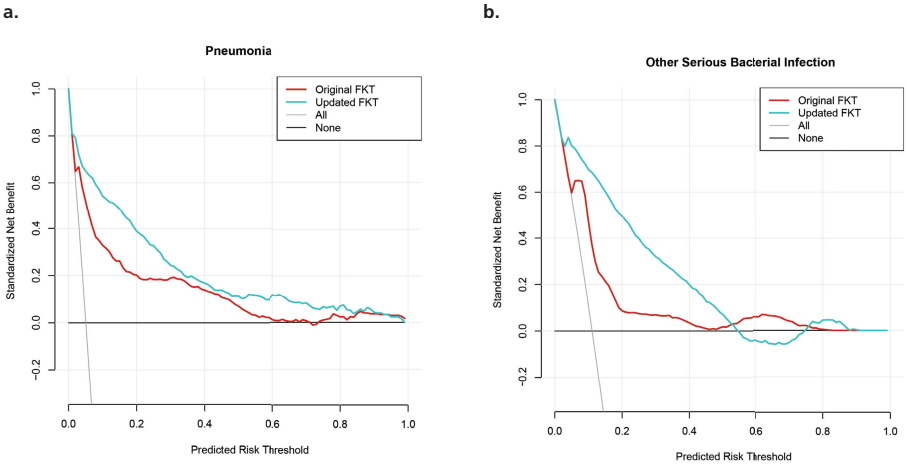
The recalibrated original Feverkidstool discriminated well between pneumonia and other infections (c-statistic 0.84, 95% CI 0.77 to 0.92), and between other SBIs and other infections (c-statistic 0.82, 95% CI 0.77 to 0.86, online supplementary figure 2). This performance is similar to previous Feverkidstool validations.[11,12] Updating the Feverkidstool with the assay improved discrimination between bacterial and other infections, reflected by an improved c-statistic for pneumonia to 0.89 (95% CI 0.82 to 0.96), and for other SBIs to 0.91 (95% CI

0.87 to 0.94) (online supplementary figure 2). A sensitivity analysis of the cohort without imputed reference standard diagnoses showed similar results, with improved prediction of pneumonia and other SBIs (online supplementary table 2).

Predicted risk thresholds

The DCA shows the net benefit of starting antibiotics using predictions of the updated instead of the original Feverkidstool, depending on the choice of probability threshold. Children with low–moderate predicted risks ≤40% for pneumonia or other SBIs had most benefit from the updated Feverkidstool (figure 1). For example, if all children with a predicted risk of >20% would be treated with antibiotics, the net benefit of the updated Feverkidstool increases with 0.2 from the 0.2 net benefit in the original Feverkidstool for predicting pneumonia to 0.4 net benefit. For predicting other SBI the net benefit increases from 0.1 (original Feverkidstool) to 0.5 by the updated Feverkidstool. In absolute numbers this would mean that by using the updated Feverkidstool at a threshold of 20%, we achieve 20 to 50 more correct treatment decisions (out of 100 patients) than when using the original Feverkidstool. Table 2 gives more detailed insight on effects of the updated model in diagnostic value using several thresholds. Using a rule of thumb of LR+ of 5 and LR– of 0.2,[25] thresholds of 10% and 2.5% using the updated model seem better applicable for ruling in and out of both pneumonia and other SBIs.

Figure 1. Decision curve analysis



Decision curve analysis with the net benefit of starting antibiotics to none of the patients (black line), to all patients (grey line), the original Feverkidstool (red line), and the updated Feverkidstool (blue line), depending on the choice of probability threshold for starting antibiotics for pneumonia (a) and other SBI (b). FKT; Feverkidstool.

Table 2. Diagnostic performance of prediction models including clinical signs and symptoms and either C reactive protein or the assay.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR– (95% CI)
Original Feverkidstool						
Pneumonia						
Risk of ≥ 2.5%	0.85 (0.77–0.94)	0.58 (0.54–0.63)	0.10 (0.06–0.14)	0.99 (0.98–0.99)	2.06 (1.39–3.07)	0.25 (0.08–0.76)
Risk of ≥ 5%	0.81 (0.71–0.91)	0.76 (0.73–0.79)	0.15 (0.09–0.22)	0.99 (0.98–0.99)	3.41 (2.23–5.20)	0.24 (0.10–0.62)
Risk of ≥ 10%	0.62 (0.47–0.78)	0.89 (0.87–0.92)	0.24 (0.13–0.34)	0.98 (0.97–0.99)	5.83 (3.90–8.71)	0.42 (0.25–0.69)
Risk of ≥ 15%	0.48 (0.31–0.65)	0.93 (0.91–0.95)	0.27 (0.14–0.40)	0.97 (0.96–0.98)	6.80 (3.87–11.97)	0.56 (0.37–0.84)
Risk of ≥ 20%	0.40 (0.23–0.58)	0.95 (0.94–0.97)	0.31 (0.16–0.47)	0.97 (0.96–0.98)	8.52 (4.57–15.90)	0.63 (0.45–0.87)
Risk of ≥ 30%	0.27 (0.10–0.45)	0.99 (0.98–1.00)	0.60 (0.39–0.81)	0.96 (0.95–0.98)	28.09 (8.16–96.67)	0.73 (0.57–0.94)
Other SBIs						
Risk of ≥ 2.5%	0.98 (0.97–1.00)	0.19 (0.15–0.22)	0.13 (0.10–0.16)	0.99 (0.98–1.00)	1.21 (1.13–1.30)	0.09 (0.01–0.65)
Risk of ≥ 5%	0.96 (0.94–0.99)	0.41 (0.37–0.46)	0.17 (0.13–0.21)	0.99 (0.98–1.00)	1.64 (1.48–1.83)	0.08 (0.02–0.43)
Risk of ≥ 10%	0.85 (0.78–0.92)	0.70 (0.67–0.74)	0.26 (0.20–0.33)	0.98 (0.96–0.99)	2.87 (2.37–3.48)	0.21 (0.10–0.42)
Risk of ≥ 15%	0.54 (0.42–0.66)	0.82 (0.79–0.85)	0.27 (0.19–0.36)	0.94 (0.92–0.95)	3.03 (2.24 (4.12)	0.56 (0.41–0.76)
Risk of ≥ 20%	0.38 (0.26–0.50)	0.89 (0.86–0.91)	0.30 (0.19–0.40)	0.92 (0.90–0.94)	3.37 (2.23–5.09)	0.70 (0.57–0.86)
Risk of ≥ 30%	0.25 (0.13–0.36)	0.94 (0.92–0.95)	0.32 (0.18–0.46)	0.91 (0.89–0.93)	3.82 (2.15–6.77)	0.81 (0.69–0.93)

Table 2. (continued)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR– (95% CI)
Updated Feverkidstool						
Pneumonia						
Risk of ≥ 2.5%	0.88 (0.80–0.95)	0.75 (0.71–0.78)	0.16 (0.09–0.22)	0.99 (0.99–1.00)	3.48 (2.39–5.07)	0.16 (0.05–0.49)
Risk of ≥ 5%	0.85 (0.76–0.94)	0.83 (0.80–0.86)	0.21 (0.13–0.29)	0.99 (0.99–1.00)	4.93 (3.55–6.84)	0.18 (0.07–0.49)
Risk of ≥ 10%	0.76 (0.64–0.88)	0.89 (0.86–0.91)	0.27 (0.17–0.37)	0.99 (0.98–0.99)	6.84 (4.49–10.41)	0.27 (0.14–0.53)
Risk of ≥ 15%	0.72 (0.60–0.85)	0.92 (0.90–0.94)	0.33 (0.21–0.45)	0.98 (0.98–0.99)	9.27 (5.47–15.72)	0.30 (0.15–0.58)
Risk of ≥ 20%	0.66 (0.52–0.80)	0.94 (0.93–0.96)	0.39 (0.25–0.53)	0.98 (0.97–0.99)	11.88 (7.07–19.97)	0.36 (0.20–0.63)
Risk of ≥ 30%	0.50 (0.34–0.67)	0.97 (0.96–0.98)	0.48 (0.31–0.65)	0.97 (0.96–0.98)	17.45 (8.88–34.27)	0.50 (0.31–0.82)
Other SBIs						
Risk of ≥ 2.5%	0.97 (0.94–0.99)	0.62 (0.58–0.66)	0.24 (0.19–0.30)	0.99 (0.99–1.00)	2.57 (2.22–2.99)	0.05 (0.01–0.26)
Risk of ≥ 5%	0.92 (0.88–0.97)	0.75 (0.72–0.79)	0.32 (0.25–0.39)	0.99 (0.98–1.00)	3.71 (3.04–4.51)	0.10 (0.04–0.26)
Risk of ≥ 10%	0.88 (0.82–0.94)	0.83 (0.80–0.86)	0.39 (0.31–0.47)	0.98 (0.97–0.99)	5.05 (4.04–6.32)	0.15 (0.07–0.30)
Risk of ≥ 15%	0.84 (0.77–0.91)	0.86 (0.84–0.89)	0.43 (0.35–0.52)	0.98)0.97–0.99)	6.16 (4.78–7.93)	0.18 (0.10–0.34)
Risk of ≥ 20%	0.80 (0.72–0.88)	0.89 (0.86–0.91)	0.46 (0.37–0.56)	0.97 (0.96–0.98)	6.95 (5.27–9.17)	0.22 (0.14–0.37)
Risk of ≥ 30%	0.67 (0.57–0.77)	0.91 (0.89–0.93)	0.49 (0.39–0.59)	0.96 (0.94–0.97)	7.70 (5.49–10.82)	0.36 (0.25–0.52)

LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SBI, serious bacterial infection.

Reclassification

Table 3 shows the clinical consequences if the updated Feverkidstool was used instead of the original Feverkidstool. In total, the updated Feverkidstool for pneumonia reduced the number children with a falsely predicted high or intermediate risk from 234 to 143 (39%) compared to the original Feverkidstool, and from 427 to 197 (54%) for children with other SBI.

Table 3. Diagnostic reclassification by the updated Feverkidstool compared to the original Feverkidstool

a.		**Reference standard diagnosis: Pneumonia (n=30)**			**Reference standard diagnosis: No pneumonia (n=561)***		
		Updated Feverkidstool predicted risk for pneumonia			***Updated Feverkidstool predicted risk for pneumonia***		
		Low	Intermediate	High	Low	Intermediate	High
Original Feverkidstool predicted risk for pneumonia‡	Low	3	1	1	304	20	3
	Intermediate	1	2	4	100	46	27
	High	0	0	18	14	14	33

b.		**Reference standard diagnosis: Other SBI (n=66)**			**Reference standard diagnosis: No other SBI (n=525)†**		
		Updated Feverkidstool predicted risk for other SBI			***Updated Feverkidstool predicted risk for other SBI***		
		Low	Intermediate	High	Low	Intermediate	High
Original Feverkidstool predicted risk for other SBI§	Low	1	0	0	98	0	0
	Intermediate	1	2	6	190	55	25
	High	0	4	52	40	51	66

The Feverkidstool classification was compared to the majority reference standard for the prediction of pneumonia (A) and other SBIs (B). Head-to-head comparison of the original Feverkidstool and the updated Feverkidstool. Predicted risks of pneumonia (A) and other SBIs (B) were low if the predicted risk was below 2.5%, intermediate between 2.5% and 10%, and high above 10%.

**As the comparison in this table is between the presence or absence of pneumonia, it should be noted that 'no pneumonia' includes viral and other SBIs.*

***†**As the comparison in this table is between the presence or absence of other SBI, it should be noted that 'no other SBI' includes viral and pneumonia.*

***‡**Among the patients with a pneumonia as determined by the majority of the expert panel, six patients were correctly reclassified as being at higher risk using the updated Feverkidstool instead of the original Feverkidstool and one patient was incorrectly reclassified. For patients in whom pneumonia was absent, these numbers are respectively 128 and 50. Reclassification improvement was 17% for patients with pneumonia (6 minus 1 of 30) and 14% for patients without pneumonia (128 minus 50 of 561).*

§Among the patients with other SBI as determined by the majority of the expert panel, six patients were correctly reclassified using the updated Feverkidstool instead of the original Feverkidstool and five patients were incorrectly reclassified. For patients in who other SBIs are absent, these numbers are respectively 281 and 25. Reclassification improvement was 2% for patients with other SBIs (6 minus 5 of total 66) and 49% for patients without other SBIs (281 minus 25 of 525).

SBI, serious bacterial infection.

DISCUSSION

In this study, we showed that when a clinical prediction model including CRP was updated with a combined host-protein based assay, SBIs were predicted more accurately in children presenting with a lower RTI or FWS at the hospital. We showed that children with a low-to-moderate predicted risk benefit most from this updated model.

Strengths and weaknesses of the study

A strength of the present study is the used combination of variables. To our knowledge, this is the first study combining clinical parameters with both bacterial and viral biomarkers. A second strength is the use of an expert panel reference standard, which has the advantage of capturing a wide spectrum of illness severities, including difficult to diagnose cases, thereby reflecting the diagnostic process in clinical practice.[26] Another strength is the prospective patient recruitment. The ethics committees approved venous blood sampling even if blood sampling was not indicated for routine care. Therefore, a wide spectrum of illness severity was captured, including difficult to diagnose cases. In addition, a strength of the Feverkidstool is its polytomous character. This enables the discrimination between different diseases: pneumonia and other SBIs versus no SBIs.[27] Finally, in clinical practice different thresholds are needed depending on the setting. Therefore we performed a DCA to help interpret the differences between the models along the wide range of predicted probabilities.[20]

Limitations of our study should also be addressed. First, the number of bacterial cases was relatively low. Therefore, it was not possible to refit the individual coefficients for all Feverkidstool variables. The aim of the current study was to see whether the new assay had additional value to the original well validated Feverkidstool rather than to build an optimal diagnostic model. Second, one of the Feverkidstool variables, capillary refill, was not available for any of the participants. Therefore, multiple imputation was impossible. Leaving capillary refill out by entering 0 for all capillary values would have resulted in an unfair reduction of model calibration. We think imputation of the mean was the best available option.[24] Even though this may have limited the discriminative performance of the model, we believe the influence is limited, because the dichotomous variable capillary refill has little diagnostic value within the Feverkidstool. In addition, the aim of the current study was to compare the original Feverkidstool with the updated model. Imputation of capillary refill values was performed similarly for both models, so this had no influence on the comparisons of the models. Third, the reclassification is based on arbitrarily chosen thresholds (2.5% and 10%). These thresholds, however, mostly corresponds with LR that have been reported to be meaningful in decisions for febrile children: LR+ >5.0 for ruling-in SBIs and LR- <0.2 for

ruling-out SBIs.[25] Fourth, the Feverkidstool includes important clinical variables that are used by every physician when deciding to start antibiotics or not. Following clinical care, during the expert panel reference standard process, the panel was provided with a wide range of clinical information, including the clinical Feverkidstool variables, but they were not informed about the algorithm. We, however, cannot exclude that incorporation bias - in which part of the test being assessed is included in the reference standard - has resulted in some degree of overestimation of the outcome. Fifth, due to the relatively low number of bacterial cases, some diseases, such as bacterial meningitis, were not observed in our study cohort. Information to discriminate sepsis from bacteraemia cases was not available. Sixth, in the current study, none of the ED patients were hospitalised at the intensive care unit. Further studies with higher numbers of patients with a more severe clinical presentation are warranted as especially in these patients early detection of SBI can be critical. Seventh, in this study we wanted to study the added value of the assay on top of the model that had also undergone impact analysis[28] (ie, the original Feverkidstool (including CRP)), rather than developing a new model. As both the assay and the original Feverkidstool contain CRP, we had to solve this. Refitting the Feverkidstool's model without CRP will not provide the answer to our research question on the *added* value of the assay to the Feverkidstool. In addition, the number of bacterial cases was too low to refit the original Feverkidstool. We also did not want to simply add the assay as a predictor in the Feverkidstool model, as this would downwardly bias the assay's added value. Therefore, we essentially removed the effect of the CRF in the Feverkidstool by assigning the median value of CRP to the CRP single predictor in the Feverkidstool to all patients. To our knowledge, using the median CRP was the best possible approach to avoid double counting of CRP. Finally, there were 71 patients for whom the expert panel could not assign a final diagnosis. Such inconclusive cases are inherent to studies using outcomes lacking a gold standard. To make optimal use of the data from all recruited patients, we have imputed these reference standard diagnoses. As the imputed diagnoses are used for both the original and the updated Feverkidstool, we do not expect this influenced the results of updating the Feverkidstool. In addition, a sensitivity analysis in which all cases with imputed diagnoses were excluded showed comparable results.

Comparison with existing literature

The study in which the Feverkidstool was developed and the OPPORTUNITY Study had comparable inclusion criteria. Most importantly, both studies included children suspected of infection based on increased temperature.[12,14] Differences in inclusion criteria should also be discussed. The Feverkidstool derivation cohort included Dutch children aged 1 month to 15 years, whereas the OPPORTUNITY Study included Dutch and Israeli children aged 1 month to 5 years. In addition, for the Feverkidstool development study children who received

antibiotics before the ED visit were excluded; for the OPPORTUNITY Study antibiotic use was no exclusion criterion.[12,14]

We recently confirmed the external validity of the Feverkidstool, but when procalcitonin (PCT) was added to the prediction model or when CRP was replaced by PCT the accuracy for predicting SBIs in febrile children did not improve.[11] Another study updated the Feverkidstool by adding PCT and resistin, resulting in minimal changes in LR+ and LR- for different risk thresholds.[13] In contrast to the two above mentioned Feverkidstool updates, our current study has shown that updating the Feverkidstool with the assay does meaningfully improve the accuracy of the model. This further confirms our previous observation that the combination of CRP, TRAIL and IP-10 had higher diagnostic value in differentiating between bacterial and viral infections compared to PCT or CRP alone.[14]

Implications for clinical practice

Clinical signs and symptoms play an important role when physicians diagnose febrile children, but do not sufficiently differentiate between viral and bacterial infections. Therefore, the use of diagnostic prediction models that include both clinical parameters and biomarkers is intuitive and helpful. The Feverkidstool provides two risk percentages; the risk for having pneumonia and the risk for having other SBIs. After further validation, a digital calculator should be constructed to facilitate potential clinical use. Both the assay and the Feverkidstool are designed to predict the outcome 'bacterial infection', and not the general level of illness of the child. Therefore, the outcome can be used to guide decisions on starting antibiotics or not, but cannot be used to guide decisions on how to administrate antibiotics or what type. We showed that the updated Feverkidstool has most added value for patients in the low-moderate risk group, with predicted risk for SBI below 40%. At thresholds of 2.5% and 10%, the reclassification table showed substantial improvement in diagnosis. The cases with predicted risks between low to moderate (2.5 vs 40%) may be characterized by having intermediate values of CRP with higher diagnostic uncertainty. Adding two viral biomarkers to the prediction rule will provide an extra dimension to the model and therefore improves diagnosis especially for those cases. As a point-of-care test is under development, the manufacturer has not given an indication to the eventual cost yet. To optimize cost-effective use of the combination test, our results suggest that the added value of the assay is the highest in children with a predicted risk <40% as predicted by the original Feverkidstool. Utility studies are needed to determine the cut-off for the best clinical utility and cost-effectiveness.

Implications for future research

Since we have proven the accuracy of the updated Feverkidstool, the next step is to perform a prospective external validation, and to evaluate its impact on resource use and antibiotic treatment. An important aspect is to define risk cut-offs for different settings in clinical practice, for example, young children and children with comorbidities. In addition, in order to optimize resource use, new biomarkers may benefit selected patient subgroups in particular (eg, selected on a set of clinical characteristics/predicted risk) rather than in all febrile children. This targeted risk approach may also be applied to position the role of e.g. Myxovirus resistance protein A (MxA) and CRP.[29]

Conclusion

In conclusion, a new blood assay including viral and bacterial biomarkers, combined with a clinical prediction model, is in this study cohort, superior to the model with CRP only for predicting SBIs in preschool children. In children with low-to-moderate predicted risk of SBI in particular, the updated Feverkidstool with the assay has the potential to optimize targeted antibiotic prescription and to prevent unnecessary use of antibiotics.

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SUPPLEMENTARY FILES

Available on the BMJ Paediatrics Open website:

- Statistical analysis plan
- TRIPOD reporting guideline checklist

Figure 1. Flowchart of included patients

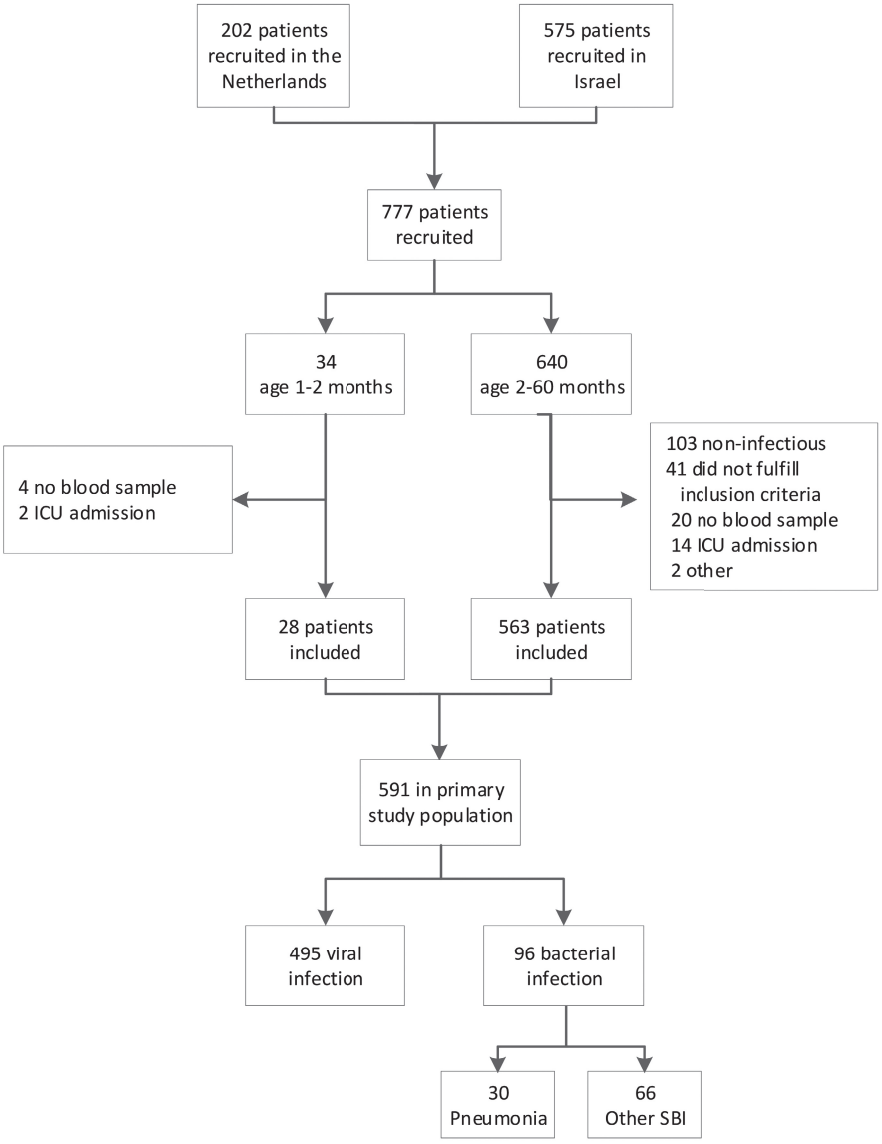

Figure 2. Receiver operating characteristics (ROC) curve of sensitivity versus specificity for the original and updated Feverkidstool.

Area under the receiving operating curve (c-statistic) for the original and for the updated Feverkidstool for pneumonia and other SBI are shown in the figure. The c-statistic difference for pneumonia is 0.09 and 0.05 for other SBI. FKT: Feverkidstool, SBI: serious bacterial infection.

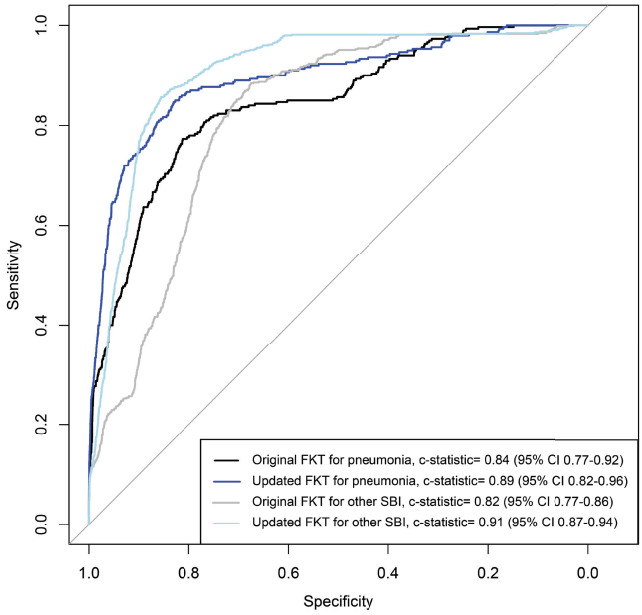

Table 1. Characteristics of patients with and without reference standard
Clinical syndrome was based on the diagnosis of the attending physician at discharge from the hospital. LRTI included pneumonia and bronchiolitis; URTI included laryngitis, pharyngitis, otitis media, sinusitis and tonsillitis. Baseline characteristics of excluded patients are shown in the supplementary material. *p-values of differences between bacterial and viral infections.

	Viral and bacterial reference standard diagnosis (n=520)	Inconclusive reference standard diagnosis (n=71)	p-value
Predictor variables			
Age (years), median (IQR)	1.2(0.6-2.4)	1.7(1.0-3.0)	0.01
Gender, male, n (%)	289(56%)	42(59%)	0.61
Duration of fever (days), median (IQR)	2(1-4)	2(1-4)	0.80
Temperature (°C), median (IQR)	38.5(37.7-39.2)	38.6(37.8-39.3)	0.49
Respiratory rate, mean (SD)	42(16)	39(12)	0.35
Tachypnea, n (%)	140(27%)	19(27%)	0.74
Heart rate, mean (SD)	152(24)	151(25)	0.92
Tachycardia, n(%)	248(48%)	34(48%)	0.77
Oxygen saturation %O_2, median (IQR)	98(97-100)	98(96-100)	0.41
Desaturation, <94%O_2, n (%)	25(5%)	0(0%)	0.10
Chest wall retractions, n (%)	67(13%)	3(4%)	0.045
Ill appearance, n (%)	153(29%)	26(37%)	0.22
C-reactive protein (mg/l), median (IQR)	18(7-46)	53(18-83)	<0.001
Assay score, median (IQR)	7(1-40)	35(5-88)	<0.001
Other variables			
Hospital admission n (%)	290(56%)	38(54%)	0.70
Hospitalization duration (days), median (IQR)	3(2-4)	3(2-5)	0.08
Antibiotic treatment prescribed n (%)	180(35%)	53(75%)	<0.001
Recruiting site			0.80
Secondary care centre, n (%)	487(94%)	66(93%)	
Tertiary care centre, n (%)	33(6%)	5(7%)	
Clinical syndrome			0.21
Bacteraemia /viraemia	10(2%)	1(1%)	
Central nervous system	9(2%)	0(0%)	
Fever without source	164(32%)	16(23%)	
Gastro-enteritis	19(4%)	1(1%)	
Lower respiratory tract infection	127(24%)	17(24%)	
Upper respiratory tract infection	127(24%)	23(32%)	
Urinary tract infection	22(4%)	2(3%)	
Other	42(8%)	11(16%)	

Table 2. Sensitivity analysis of the cohort without imputed reference standard diagnoses
Presented data are c-statistics and 95% confidence intervals

	Pneumonia	Other SBIs
Original Feverkidstool	0.87(0.79-0.95)	0.82(0.76-0.88)
Updated Feverkidstool	0.91(0.83-0.98)	0.91(0.86-0.95)

Table 3. Description of recalibration of the Feverkidstool and the updated model
Linear predictors for pneumonia and other SBI Feverkidstool are calculated as defined previously [1]:

LP (pneumonia Feverkidstool*) = -17.9 (Intercept) + 1.02 * Age (max 1 year, in years) + 0.01 * Age (if >1 year: age in years - 1)+ 0.13 * Sex (female) + 0.29 * Temperature (°C) + 0.21 * Duration of fever (days) + 0.44 * Presence of tachypnoea - 0.04 * Presence of tachycardia + 1.59 * Oxygen saturation <94% - 0.18 * Capillary refill time (>3s) + 0.47 * Presence of chest wall retractions + 0.16* ill appearance + 0.64 * Ln(CRP) (mg/l)*

LP (other SBI Feverkidstool*) = -4.7 (Intercept) -1.73 * Age (max 1 year, in years) + 0.11 * Age (if >1 year: age in years – 1)+ 0.70 * Sex (female) - 0.02 * Temperature (°C) - 0.03 * Duration of fever (days) - 0.11 * Presence of tachypnoea - 0.02 * Presence of tachycardia - 3.29 * Oxygen saturation <94% + 0.30 * Capillary refill time (>3s) - 3.78 * Presence of chest wall retractions + 0.27 * ill appearance + 1.14 * Ln(CRP) (mg/l)*

where LP refers to the linear predictor in a (polytomous) logistic regression model.

We used the fixed intercept and coefficients within the original Feverkidstool, but used the outcome as a linear predictor in our logistic recalibration model and in the updated model. This resulted in the following (polytomous) logistic regression models:

Recalibration of original Feverkidstool:
LP1 = -0.58 + 1.28 (LP pneumonia Feverkidstool)
LP2 = -0.02 + 0.54 (LP other SBI Feverkidstool)

Updated Feverkidstool, including combination assay:
LP3 = -4.19 + 0.59 (LP pneumonia Feverkidstool, with median CRP for all patients)+ 0.05 (score Assay)
LP4 = -3.57 + 0.24 (LP other SBI Feverkidstool, with median CRP for all patients)+ 0.05 (score Assay)

Probabilities of the outcomes are calculated with:
Original Feverkidstool Risk (pneumonia) = $e^{LP1}/ (1 + e^{LP1} + e^{LP2})$
Original Feverkidstool Risk (other SBI) = $e^{LP2} / (1 + e^{LP1} + e^{LP2})$,
Updated Feverkidstool Risk (pneumonia) = $e^{LP3} / (1 + e^{LP3} + e^{LP4})$
Updated Feverkidstool Risk (other SBI) = $e^{LP4} / (1 + e^{LP3} + e^{LP4})$, [2, 3]

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Chapter 4.

Supporting parents' decisions for their child with fever

Chapter 4.1.

Development and evaluation of a hospital discharge information package to empower parents in caring for a child with a fever

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ABSTRACT

Objectives

First, to explore parents' views on and experiences of managing their febrile child and to assess their behaviour and needs when in search of information about fever; second, to develop and evaluate a hospital discharge information package about fever in children.

Design

Mixed methods: (A) qualitative study with semistructured interviews and a focus group discussion (FGD) and (B) quantitative survey.

Setting

Emergency department, non-acute hospital setting and day nursery in Rotterdam, The Netherlands.

Participants

Parents of children <18 years (interviews, n=22), parents of children under 5 years (FGD (n=14), survey (n=38)).

Intervention

Information package about fever in children (leaflet and website including videos).

Outcome measures quantitative survey

Knowledge of fever and confidence in caring for a febrile child (Likert scale 0–5).

Results

Parents found fever mostly alarming, especially high fever. Help-seeking behaviour was based on either specific symptoms or on an undefined intuition. When parents did not feel recognized in their concern or felt criticised, anxiety increased as well as the threshold to seek healthcare for future illnesses. Information was needed, especially for situations when the general practitioner or social network were less easily available. This information should be reliable, consistent, available in multiple formats and include advice on management of fever at home and precise referral to medical services. Parents reported improved knowledge about fever ($p<0.05$) and mentioned improved confidence in caring for a child with fever at home after consulting the information package.

Conclusion

Parents of children with a fever visiting the hospital are concerned about specific symptoms or based on an undefined intuition. Rather than telling parents that they should manage their child's illness at home, healthcare professionals should recognize parental intuition and provide clear information on alarming signs and potential diagnoses to empower parents in the management of their febrile child.

INTRODUCTION

Fever in children is the most frequent reason for parents to seek medical attention.[1,2] The majority of these children are under 5 years and have a self-limiting disease. In general practice, around 1% have a serious infection; in an emergency department (ED), this is 5%–15%; the most frequent serious infection being pneumonia.[3,4] However, the number of ED admissions continues to increase, mostly for minor illness not needing intervention.[5,6]

The current problem is twofold:

1. Parents are well capable of identifying their ill child by describing how their child's illness differs from previous episodes (parental intuition or gut feeling).[3] However, this parental concern is non-specific and also present in non-severe illness.[7] Potential reasons might be a lack of knowledge about fever and anxiety about potential harmful consequences.[8,9]
2. At the same time, there are still children dying of serious infections due to errors or delays in diagnosis.[10] As serious infections often cannot be distinguished from self-limiting disease at an early stage, it is important that parents recognise warning signs during the disease course.

In order to reduce unnecessary ED consultations for self-limiting disease, but also to prevent parents from missing a seriously ill child, parents need clear hospital discharge advice about managing their febrile child at home. For this advice to be effective, it should fit well with parent's needs and worries.[11] Even though studies have been done in general practice and in well-child clinics,[12,13] knowledge on the necessary information about fever for parents visiting the ED is limited.

The aims of the study are to: (A) explore parents' views on, and experiences of, managing their febrile child; (B) to assess their behaviour and needs when in search of information about fever; and (C) to develop and evaluate a hospital discharge information package about fever in children.

METHODS

Study design

This was a two stage project, using exploratory theory building methods for stage 1 (development), followed by an intervention and evaluation for feasibility and piloting in stage 2. This methodology follows the Medical Research Council (MRC) framework for development and evaluation of complex interventions.[14]

Development

A qualitative design was used to explore parents' views on, and experiences of, fever in children through the use of semistructured interviews. Based on these findings, we developed an information package, consisting of a leaflet (online supplementary file 1) and a website (www.sehzorg.nl/koortskinderen (in Dutch)), both of which included a traffic light system to help parents identify the risk of serious illness after hospital discharge. The website also contained informative videos about fever and pneumonia in general and videos illustrating warning and safety signs in febrile children.

Feasibility and piloting

The complete information package was evaluated to assess its feasibility during a focus group discussion (FGD) with parents of children under 5 years. Emerging themes that arose during the development phase were also further explored in the FGD. In addition, a quantitative survey was used to evaluate the information package in a pilot in the acute and non-acute setting.

Sampling and recruitment

Development

We recruited a purposive sample of parents of children under 16 years for the interviews, both in an acute setting (at the ED) and in a non-acute setting (outpatient department or ward), to obtain maximum variation within the sample. All interview participants were recruited in the Erasmus Medical Centre – Sophia Children's Hospital (EMC-Sophia) and the Maasstad Hospital, Rotterdam, until a point of data saturation was reached. Out of 29 eligible parents, 22 agreed to participate; seven refused for various reasons (no interest or time and language barrier).

Feasibility and piloting

We recruited parents of children under 5 years for the FGD through an open invitation at day nurseries (digitally and by posters on location) in the Rotterdam area, through social

media of patient organization Kind en Ziekenhuis (K&Z) and EMC-Sophia, and an article in a regional newspaper.[15] Participants for the quantitative survey were recruited at the ED of the EMC-Sophia, through day nurseries and by open invitation on the information website between July and October 2017.

Research team

The core research team (all female) consisted of an MD/PhD student in paediatrics (JvdM), medical students (DvK and AdH) and a consultant in paediatrics (RO (MD, PhD)). JvdM was trained in qualitative methodology and we shared expertise with an international expert in this research area and methods (ML (MD, PhD)) and with a social scientist from patient organisation K&Z (ES-C).

Data collection

Development

DvK conducted the semistructured interviews between November 2016 and February 2017 in a hospital room with only the researcher and the participant, using a flexible interview guide (online supplementary file 2). All interviews were audio recorded. The relatively short duration of 15 minutes generated sufficient information and facilitated participation, since they took place during waiting time in the hospital.

Feasibility and piloting

The FGD was held in February 2017 at an inner city nursery near the EMC-Sophia. We chose this setting as a more neutral and more natural environment for parents than a medical setting in order to promote open and rich conversation and to reduce the risk of social desirability bias. ES-C and JvdM led the FGD, using a discussion guide including open questions and example cases (online supplementary file 3). RO and DvK had an observer's role and interacted occasionally if needed. The FGD was audiorecorded and lasted 2 hours. For the quantitative evaluation, we used a survey with questions on: (1) knowledge about fever in children and about caring for a febrile child at home (questions 1–3) and about parents' confidence in their ability to provide adequate care for a febrile child and in their ability to seek medical attention (questions 4–6), referring to the situation before and after consulting the information package.[16] In addition, questions were asked about clarity and layout of the information package (online supplementary file 4). Demographic information was collected from all participants.

Data analysis

All interviews and the FGD were transcribed verbatim by DvK, including non-verbal information. An interim analysis of 14 interviews guided further exploration of the emerging themes in subsequent interviews. Thematic content analysis was used for all interviews and the FGD, using the qualitative software package Atlas.ti (V.7.5.7.).[17,18] First, the fully transcribed interview/FGD was read in detail, then meaning units were defined and coded. Initial themes were combined into overarching themes, containing subthemes reflecting their components (figure 1). A pilot of three transcribed interviews and the complete FGD were coded by two authors independently (DvK and JvdM) and final codes and themes agreed on. The scores on the Likert scale of the quantitative survey were coded from 0 to 5, mean scores were calculated and differences in pre-exposure and post-exposure scores were analysed using a paired sample t-test. Statistical code and dataset of the quantitative survey are available as online online supplementary files.

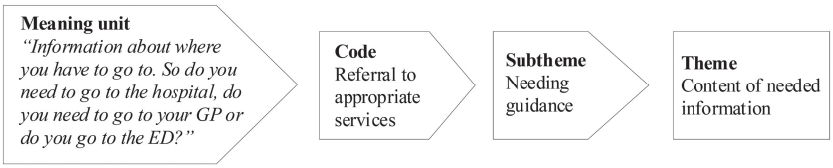

Figure 1. Coding process

Ethics

Written informed consent for the interviews and FGD was obtained from all participants.

Patient and Public Involvement

This study was performed in close collaboration with 'Kind en Ziekenhuis', a patient organization for children in hospitals, representing the patient's perspective in study design, protocol development and conduction of the study. We developed and updated the intervention based on parent's views and needs, as described in this paper. The intervention is publicly available to all end-users.

RESULTS

Participants

A total of 22 semistructured interviews were performed, half in acute setting and half in a non-acute setting (6 men, 16 women). Fourteen women participated in the FGD (13 mothers, 1 aunt). The survey included 38 parents. Baseline characteristics of all participants are presented in table 1. Overall, most participants were female, with a median age between

33 and 35 years. The participants of the FGD were all female, had less children and younger children than the other participants. There were no differences between participants in the acute or non-acute setting of the interviews and survey, in terms of gender, age and number of children.

Table 1. Participant characteristics

	Semistructured interviews (n = 22)	**Focus group discussion (n = 14)**	**Survey study (n = 38)**
	n (%)	n (%)	n (%)
Acute setting (ED)	11 (50)	0	10 (26)
Non-acute setting	11 (50)	14 (100)	28 (74)
Frequency of hospital consultation			
<5 times	16 (73)	na	na
>5 times	6 (27)	na	na
Has chronically ill child	4 (18)	1 (7))	na
Female	16 (73)	14 (100)	35 (92)
Median age in years (range)	35 (19-48)	33 (26-42)	34 (26 - 52)
Median number of children (range)	2 ((1-6)	1 (0-3)*	2 (1-6)
Median age of children in years (range)	6 (0-22)	2 (0-9)	category: 2 - 5
Highest education			
Primary or secondary school	3 (14)	1 (7)	
Community college / Intermediate vocational education	11 (50)	4 (29)	6 (60)†
College or University	8 (36)	9 (64)	4 (40)†
Occupation			
Full time working	8 (36)	6 (43)	na
Part time working	8 (36)	7 (50)	na
Housewife/houseman	6 (27)	1 (7)	na
Country of birth			
Netherlands	19 (86)	13 (93)	5 (50)†
Other‡	3 (14)	1 (7)	5 (50)†
Country of birth parents			
Netherlands	13 (59)	11 (79)	na
Netherlands - other‡	0	2 (14)	na
Other - other‡	9 (41)	1 (7)	
Median understanding Dutch language (scale 0 - 10, range) §	10 (6-10)	10 (8-10)	10 (8 - 10)†

** 1 participant came with sister (present as an aunt)*

† only available for participants in acute setting (n=10)

‡ including: Morocco, Suriname, Turkey, Cape Verde, Pakistan, Poland, Indonesia, Italy

§ 0 = no understanding of Dutch language, 10 = excellent understanding of Dutch language

Development phase

The interviews and FGD results can be divided into three main content areas: (A) views on fever and its treatment, (B) experiences of managing a child with a fever and (C) information seeking. Codes and (sub)themes are reported in online online supplementary file 5.

Views on fever and its treatment

Views on (causes of) fever

Most parents believed fever is caused by an infection. Parents with higher levels of education mainly mentioned viruses or bacteria as a cause of infection; those with less formal education were less likely to report the exact cause. Many parents recognized fever as a natural defence mechanism of the body, but it was perceived as both reassuring and alarming: *"there's a bacterium in the body that doesn't belong there and by means of fever, you know, your body tries to destroy the bacterium. (…) But well, if it's getting too high, you know… I've heard stories like: when it's getting higher than 40, then it's going to be dangerous."* (father, three children, 5–10 years).

Views on paracetamol and antibiotics

Although with different views, most parents considered paracetamol safe to lower the temperature and relieve discomfort for the child. One mother was worried about its effectiveness when used too often: *"A slightly increased temperature… you can also give it too soon, I'm talking about high fever. (…) Otherwise they don't work anymore later on"* (mother, two children, 4-6 years).

Parents had different views on antibiotics, often depending on their own experiences. Most parents mentioned it was indicated 'only when really needed', but with different explanations. *"I think it's a last choice, like: there's nothing else, so let's go for antibiotics."* (mother, 1 child, 2 years); *"You [the doctor at the ED] saw his ears, I came urgently by ambulance because he had a febrile fit. Then at least you can give antibiotics!"* (mother, 3 children, 1–10 years). Two parents mentioned fear for resistance: *"At a certain time your body just becomes resistant, so if you just keep on taking it…"*(mother, three children, 1–14 years). One parent thought doctors were too conservative in prescribing antibiotics: *"The whole attitude of waiting too long with antibiotics, I don't agree with that at all. Not to stuff them with antibiotics immediately, but I think nowadays it is too restrained.."* (mother, two children, 4–5years).

Experiences of managing a child with a fever

Management of fever at home

Parents mentioned being more alert once they knew their child had a fever: paying extra attention to the child and looking for accompanying symptoms. Most parents try to lower the temperature with paracetamol, but homeopathic medicines were also mentioned, and removal of clothes, cold showers or cold wipes. Parents used paracetamol in various ways: (A) waiting for signs that the child is unwell, *"I almost never give paracetamol. Because I think: the body has to do it on its own and only if they develop such things as pain… But 9 times out of 10 it just resolves by itself."* (mother, three children, 2–9 years); (B) as soon as there is a fever, *"Yes, I give paracetamol when there is fever. And then every 6 hours. I try to avoid peaks to help her hopefully a bit."* (mother, one child, 9 months); or (C) based on the child's preference *"We use those suppository things, but he hates them anyway, so.."* (father, two children, 4–6 years).

Help-seeking decisions

Parents decided upon seeking medical attention based on their instincts, often difficult to specify: "*It's just a feeling. I couldn't say: one time the fever is less but he looks more ill, while another time he has 39.5 but alert. It is very much just a feeling"* (mother, FGD). *"It is a sort of gut feeling, you really feel when your child is ill. (…) I cannot describe what it is, but I know there's something wrong. And then you just want someone to look at him and be reassured"* (mother, FGD). Specific reasons to be alarmed and seek medical attention were young age (not able to express themselves), high fever, long duration of fever and accompanying symptoms like reduced appetite or drowsiness.

Learning about (managing) fever

Many parents mentioned their experience with illness in previous children or in their social background and network as a motivation for their behaviour. *"It is out of experience and it depends on your personal situation. What family you're from, what social network you have, if you have any friends… Parents from school whom you can ask questions…"* (mother, five children, 1–8 years). Especially during the FGD the role of experience was prominent, and how it can affect behaviour. One mother: *"My children have fever very often (…), but at a certain moment you get used to it. You think: I know a paracetamol works in my children, so I give it to him. (…). They have fever so often, it doesn't surprise me anymore."* Most parents recognized this. But another mother on this topic: *"sometimes I wait longer with the second child, but then he appears to have a pneumonia and then I think: I should have gone earlier".* And a mother with a first child suffering from febrile fits: *"Febrile fits run in*

families, so when I would have a second child with fever, I would be extra stressed out. But that depends on what you're used to."

Experiences with healthcare

Parental concern or instinct was often not recognised by healthcare professionals. *"When your mother feeling says: hey, something is wrong here. Then it is frustrating when a doctor says: no, there's nothing wrong."* (mother, FGD). Several parents described that when doctors say 'it's just a fever', they give parents the feeling they are not listened to or that they should not have come. *"As soon as you call the GP, they say: 'yes, but fever is normal for a child'. Then I think: you don't even listen to my story (…), first listen to what I have to say, because I don't only call because he has a fever!"* (mother, three children, 5–10 years).

In cases of self-limiting disease, some parents said they would be more reassured when the doctor explained which (possibly severe) diseases were excluded, instead of only getting the diagnosis 'another virus'. These negative experiences increased the threshold for seeking help in the future. *"Then I thought: yes, but when I call, I will be told 'yes mam, the flu is around'. So I didn't call."* (mother, FGD). Most parents had a good relationship with their own general practitioner and felt no threshold for contacting the GP, but there was a high threshold for contacting the out-of-hours services. *"He* [own GP] *takes my child very seriously. (…) The first time he had fever (…) I thought: he is going to die! But the GP always says: it doesn't matter, if you are worried: call"* (mother, FGD). *"I find it always a bad experience(…). To go to my own GP, my experience is: hey, he will come, he knows my child. But as soon as you go to the out-of-hours services it becomes difficult. There you have to struggle for an appointment."* (father, two children, 7–8 years*).*

Information seeking

Information needs

Parents expressed their need for information about fever in children, especially before deciding to seek medical attention. *"For example in the weekend you cannot call the GP and you don't call the out-of-hours service when it's not severe. So then I look it up myself"* (mother, one child, 4 years). When asked when they need information: *"Especially on Saturday or Sunday, who should you call? Then I think: I won't call 112 [European emergency number], that's nonsense. Out-of-hours service maybe, but I find that also difficult. Then there is nobody, besides family, whom you can call"* (mother, FGD).

Some parents wanted more background information on fever, but most parents emphasized the need for clear instructions about what they can and should do at home. *"Often they only*

look at dehydration, but I would want to know if she can get something against the cold and the cough." (mother, three children, 2–9 years); *"It has to state very clearly: where do you go? First to the out-of-hours GP service, or to the emergency department (…)?"* (father, two children, 2–5 years).

Information sources

Parents reported that the internet was the most commonly used source of information at home, but mentioned lack of consistency and reliability as its pitfalls. *"I always google, but that is not always helpful, because of course you also see very contradictory things"* (mother, three children, 1–14 years). Parents also ask for advice in their social network, like family or peer parents. *"Parents from school where you can ask things, like 'my child has this, did you experience that once?' You know, a network surrounding you matters a lot"*. (mother, five children, 1–8 years).

Information delivery preferences

Parents preferred multiple different formats of information: verbal and/or written, on paper and/or online. Most parents preferred verbal information given by a doctor, given the possibility to ask questions. "*I prefer verbal information. If I don't understand something, I can ask for clarification."* (mother, three children, 1–10 years). Online information should be clearly reliable. *"Mostly the information is at those general websites, where you're overwhelmed with information. I would like the information to be linked to for example a hospital."* (mother, three children, 7 weeks–5 years).

Leaflets could be reread but are often not at hand in the acute situation; written information should also be available digitally, and audio-visual material could be supportive in addition to other means. *"I think a combination of verbal and written information is best. You read something, but you want it to be confirmed by someone who has professional knowledge. (…) Or maybe with some video support or so"* (father, two children, 7 years).

Feasibility and piloting

Based on the parents' needs and preferences that we discovered during the development phase and based on the literature, a concept hospital discharge information package was developed: a leaflet (online supplementary file 1) and a website (www.sehzorg.nl/koortskinderen), including a traffic light system for identifying the risk of serious illness. The website also included informative videos about signs and symptoms (www.sehzorg.nl/koortskinderen).

Qualitative evaluation

The parents in the FGD judged this concept package to be clear and comprehensive. They particularly appreciated the traffic light system, that included clear instructions about to the severity of symptoms. However, some parents said that reading the alarming signs could raise their anxiety, a feeling not shared by all parents. Also they expressed the need for a clear statement that whenever they are worried they should be allowed to contact a healthcare professional. The videos of clinical signs and symptoms were judged to be very informative, especially for less experienced parents. Still, they expressed the need for clear instructions concerning what to do when they identified the displayed symptoms in their child. During the FGD some parents raised their concerns about febrile fits. Even though this concern was new for some parents, all of them agreed they needed information on this issue. For this reason, this was added to the package.

Parents found the combination of the written information, videos and traffic light system most helpful. *"I just think the combination is great. That there are videos and this leaflet. Because I know for example what retractions are, because I've seen it at work, but not everyone knows it. So I think it is good to see it. And with the leaflet to decide whether to do something or not."* (mother, one child, 9 weeks).

Parents said they would be more confident in caring for their children after having read and seen the information. Also it would empower them in contacting a healthcare professional, as they could support their intuitive worry by mentioning specific signs and symptoms. *"It makes a clearer impression [on the GP]: 'I looked, she's drinking less, blabla', then you know these are important things to pay attention to."* (mother, FGD).

Parents recommended that the information should be available in the waiting rooms of general practice, postnatal clinics and on social media.

Quantitative evaluation

Parents valued the information leaflet as well as the website with videos. Parents valued the information leaflet as well as the website with videos. Mean scores on all items of self-reported knowledge and confidence before and after the information package are presented in figure 2. We observed an increase in both areas of the survey: knowledge about caring for a child with a fever (4.1–4.5 out of 5), and confidence in caring for a child with a fever at home (4.1–4.3) and in help-seeking (4.4–4.5), with significance on the area of knowledge ($p<0.05$).

Parents gave high scores for layout, comprehensibility of the language, clarity of the message and usefulness of the package (median score 5 out of 5 (IQR 4–5)).

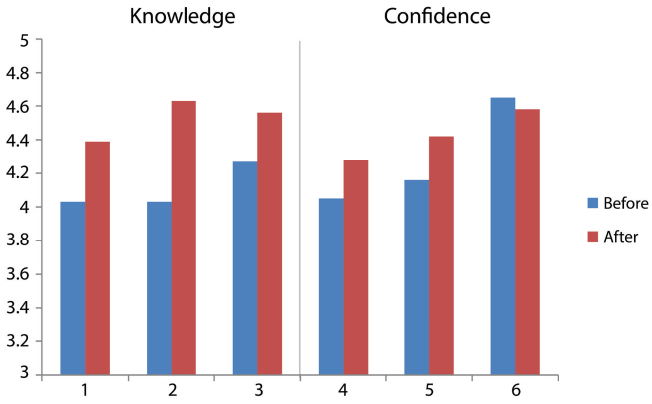

Figure 2. Knowledge and confidence before and after consulting the information package

Thematic summary

Summarizing our results, we observed that the ability of parents to care for a child with a fever after hospital discharge is influenced by many factors, as visualized in figure 3. These factors can be healthcare related or parent related, but have either an empowering or disabling influence on the parent's ability to care for their child independently. Some factors have a direct influence on parents' behaviour; other influences are more complex. For example, if a doctor dismisses parents' concerns by saying 'it is nothing' (while meaning that parents can manage this level of illness without seeking help), parents perceive this as criticism that doctors do not consider that the illness warrants medical attention. This perceived criticism increases the barrier for the parent to seek medical attention in the future.

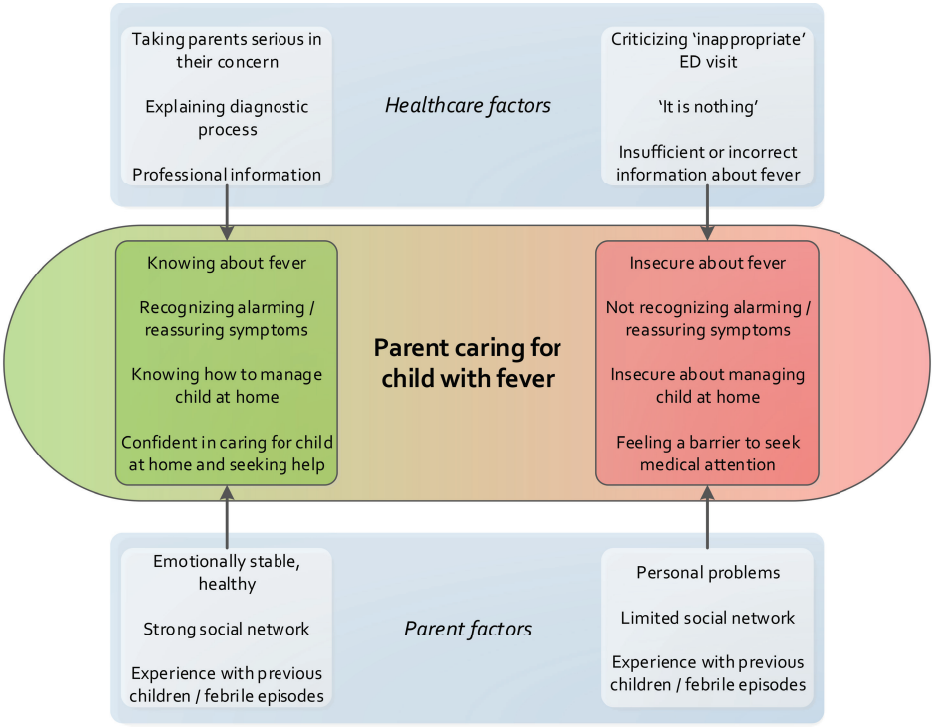

Figure 3. Positive and negative factors influencing parental ability to manage their febrile child
ED, emergency department

DISCUSSION

Main findings

Our observations in a population of parents of febrile children after hospital discharge suggest that parents in The Netherlands are concerned when their child has a fever, especially when there is a high fever. Paracetamol is perceived as a safe way to treat fever and is used in different ways. Parents preferably do not want antibiotics for their child, as they consider that they should be used 'only when really necessary', although the explanation of 'necessary' varies. Help-seeking behaviour was often based on an inexplicable parental intuition that 'something is wrong with the child', a need for reassurance, or on the presence of specific symptoms like long duration of fever, reduced appetite or drowsiness. Parents often do not feel as though they are taken seriously in their intuition or worry by healthcare professionals, and experience a high threshold for contacting healthcare during out-of-hours services.

Interpretation of findings and comparison to the literature

Even though fever was often seen as alarming, we did not find signs of 'fever phobia' and overtreatment of fever as has been described in other studies.[8,9,19,20]

Kai described earlier that help-seeking behaviour is related to the balance between perceived threat of the illness and personal control.[21] Also others noted that the ability of parents to manage a child's illness is influenced by many factors, like experience, social circumstances and expectations, and their own knowledge and health.[12,22] A recent review also described the importance of attitudes, beliefs and perceived control on the actual behaviour of seeking healthcare [23]. These dynamics are in line with our results as reflected by the balance we presented in Figure 3.

Once parents feel the need to seek healthcare, they often describe this as an intuition, which may reflect Van den Bruel's findings, where parents described their gut feeling as 'something is different than usual'.[24] However, this felt need for help by parents is not always seen as an 'appropriate' reason to visit the ED from a healthcare perspective. Ehrich described that not being aware of different meanings and viewpoints of 'appropriateness' of a medical consultation can lead to misunderstanding between doctors and parents.[25] This might partly explain the mismatch we observed between parents 'knowing something is wrong' and doctors 'saying nothing is wrong' with the child. We observed that when there is a good relationship with the doctor, he 'knows the child' and when parental intuition is taken seriously, parents feel reassured after consultation. However, when they feel criticised, or when the diagnostic process is not explained well, this may increase anxiety and increase the threshold for seeking healthcare in the future (figure 3), as also described by others.[26]

Weekends or evenings shifts with limited access to the child's own GP or their social network may be most sensitive to high thresholds for contacting the out-of-hours services, and at these moments there is a high need for information. Essential information would be practical advice about management of a child with a fever at home, and information about when to seek medical attention and where. Parents prefer information given by healthcare professionals, in addition to clear information in multiple different formats. These findings are consistent with other studies, concluding that parents' need to be reassured by receiving reliable, consistent information about fever and symptoms.[12,13,27] The role of leaflets in improving patient satisfaction after consultation has been reported in general practice.[28,29] The need for verbal explanation, supported by written and visual cues, has been reported to be most successful.[30]

Our information package including a traffic light system with instructions for management at home was deduced from the traffic light system of the NICE guideline and appreciated by the parents.[1] This system has been used before in information about respiratory tract infections and has proven its added value in informing parents.[31]

This study was mainly focused on the ED setting, thereby complementary to studies that have been performed in the setting of primary or preventive care. There are several differences between the GP setting and hospital setting, like the a priori risk of serious infection, the diagnostic value of clinical signs and symptoms,[32] the clinical experience in assessing young children and the diagnostic process. From a parent's perspective, visiting the ED is usually a stressful experience, and they mostly encounter a doctor whom they do not know. These factors emphasize even more the importance of ED healthcare professionals winning parent's trust by taking their concern seriously, clearly explain the diagnostic process and giving information that can be re-consulted after the ED visit.[33]

Strengths and limitations

The qualitative approach provided the opportunity to explore parents' views and needs in depth and to gain a better understanding of their help and information seeking behaviour. Through the use of triangulation of methods (interviews and FGD) and due to the flexible design, there was room for exploration of important themes in an open and profound way. Additional to the interviews that were well suited for exploring experiences and ideas of individual parents, the FGD enriched the data through the responses and interaction within a group.[34,35] An asset is the diversity of the participants, in terms of age, education, experience (interviews and FGD) and cultural background (interviews). A limitation is that almost all participants were fluent in Dutch reading and writing, limiting the applicability of our conclusions to parents with language-barrier or low literacy in our country or generalisation to international settings. A further limitation is that all participants of the FGD were women, a consequence of the open invitation method. However, since women are mostly the primary caregivers in The Netherlands,[36] we believe they provided rich information on help-seeking decisions. The open invitation method ensured motivated participants who were involved in the topic and could contribute to the study. To reduce the effect of a possibly intimidating hospital setting, we chose to conduct the FGD in a day nursery. Given the lively and open conversations and the fact that also negative experiences with healthcare professionals were shared, the influence of the medical background of the researchers seems limited. Our quantitative survey was limited in sample size. Also, the difference in knowledge and confidence before and after the information package was self-reported by parents, which has limitations.

Implications for clinical practice and future research

The presented positive healthcare factors from figure 3 should be implemented in clinical practice, in order to empower parents in their capacity to care for a febrile child and to support parents when they are making decisions about seeking help for their child. For healthcare providers it is essential to build a non-judgmental relationship with parents, so that they feel that they are taken seriously. Recognizing parental concern and being open about the diagnostic process (eg, explaining which potentially serious infections are excluded) could add to this. Clear hospital discharge instructions should be supported by information material that can be consulted at home. These recommendations require education of healthcare professionals and the availability of professional and clear information packages. Future research should continue to evaluate and improve information material and assess its impact. Standardized measurement tools should be developed to measure the impact of the information package on healthcare and on parent's knowledge, skills and confidence. The different ideas and needs of subgroups needs further assessment, for example migrant communities and those with limited literacy. All research should be conducted in collaboration with parents and healthcare professionals.

Conclusion

Parents of children with a fever visiting the ED are concerned about specific symptoms like long duration of fever or reduced appetite of the child, or their parental intuition says that 'something is wrong with the child'. When they perceive that their concern is not taken seriously by healthcare professionals, they feel criticised and this experience increases the threshold for future help-seeking. Rather than telling parents that they should manage their child's illness at home, healthcare professionals should recognize parental intuition and provide clear and reliable information about alarming signs, considered or excluded diagnoses, the management of fever and about available medical services. This information is needed in multiple formats, especially for moments when the doctor or social network are less available for advice. A broad information package (leaflet and website including videos) was produced in collaboration with parents and was found to increase parents' perceived knowledge about fever and improve their perceived confidence in caring for a child with fever.

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SUPPLEMENTARY FILES

Online supplementary files available on BMJ Open website

- Supplementary file 2. Interview guide semistructured interviews
- Supplementary file 3. Guide Focus Group Discussion
- Supplementary file 4. Pre and post consultation survey

Supplementary file 1. Information leaflet

Erasmus MC
Universitair Medisch Centrum Rotterdam

Sophia Kinderziekenhuis

In het Erasmus MC-Sophia is uw kind door een arts beoordeeld en heeft u advies gekregen over koorts bij uw kind. Het is belangrijk goed op te blijven letten of de situatie bij uw kind verandert. Deze folder kan daarbij een handig hulpmiddel zijn. Op de voorkant staat wat u zelf voor uw kind kunt doen. Op de achterkant staat waar u precies op moet letten bij uw kind en wat u daarbij moet doen. Binnen in de folder vindt u meer achtergrondinformatie over koorts.

Wat kunt u zelf doen?

Volg onderstaande adviezen op als uw kind koorts heeft. Wanneer uw kind normaal speelt, drinkt en plast, zijn dat geruststellende tekenen. Dit kan echter veranderen, dus het is belangrijk uw kind goed in de gaten te houden. Let daarbij op de specifieke signalen die beschreven staan op de achterkant van deze folder en volg de bijbehorende adviezen op.

- Geef uw kind genoeg te drinken, bied regelmatig kleine beetjes aan. Geef uw kind geen koolzuurhoudende dranken. Het is niet erg wanneer uw kind een paar dagen niet eet.
- Kleed uw kind niet extra warm aan, maar zorg dat het de warmte kwijt kan.
- Uw kind mag alles doen waar hij of zij energie voor heeft. Extra bedrust is niet nodig, maar laat uw kind rustig uitzieken.
- Als uw kind pijn heeft of oncomfortabel is: geef paracetamol volgens de gebruiksaanwijzing (zie ook verderop in de folder).
- Bij verkoudheid: spoel de neus een paar keer per dag met zout water, of gebruik eventueel een slijmzuiger om de neus open te houden (beide te koop bij de drogist).
- Wanneer uw kind vlekjes krijgt, doe de glastest (zie verderop in de folder).
- Het kan handig zijn per dag bij te houden wat de temperatuur van uw kind is en hoeveel uw kind plast.

Koorts bij kinderen

Voorlichtingsfilm

U kunt de film *Koorts bij kinderen, tips en adviezen voor een goed herstel* bekijken met de belangrijkste informatie over het zorgen voor uw kind met koorts. Wij raden u aan eerst de film te bekijken en dan deze folder door te lezen. U vindt de film op www.sehzorg.nl/koortskinderen.

Wat is koorts?

Wanneer de temperatuur van het lichaam boven de 38 graden komt is er sprake van koorts. Dit is een normale reactie van het lichaam op een infectie. De temperatuur kan oplopen tot boven de 40 graden en wisselen gedurende de dag of per dag. Dit zegt niets over hoe ernstig de ziekte is en komt vaak voor bij jonge kinderen.

Wat is de oorzaak?

De oorzaak van koorts is meestal een infectie. Ook kan een kind koorts krijgen nadat hij of zij een vaccinatie heeft gehad. Infecties worden meestal door een virus veroorzaakt, zoals bij verkoudheid of griep. In sommige gevallen is er echter een infectie door een bacterie. De meest voorkomende bacteriële infecties bij kinderen zijn een longontsteking of een nierbekkenontsteking. De meest ernstige infecties zijn hersenvliesontsteking of bloedvergiftiging, maar deze komen zelden voor.

Longontsteking

Bij een longontsteking zijn de kleine luchtwegen en longblaasjes ontstoken. Dit kan door een virus of een bacterie worden veroorzaakt. Een longontsteking geeft klachten als koorts, hoesten en benauwdheid en soms buikpijn. Daarnaast kunnen er ook algemene klachten zijn, zoals moeheid en niet willen eten of drinken.

Hoe weet ik dat mijn kind koorts heeft?

Als uw kind koorts heeft, voelt hij of zij warm aan. Uw kind kan moe en hangerig zijn, of minder willen eten of drinken. Ook kan uw kind last hebben van hoesten, keelpijn, buikpijn of hoofdpijn. U kunt met een thermometer de temperatuur van uw kind opmeten. Dit kan met een rectale thermometer (via de billen). Het kan ook via de oksel of mond, of met een oorthermometer. Deze zijn vooral bij baby's echter minder geschikt. Meet de temperatuur in ieder geval telkens op dezelfde manier. Als de temperatuur boven de 38 graden is, heeft uw kind koorts.

Wat is de behandeling?

Paracetamol

Koorts is op zichzelf onschuldig en het is niet nodig de temperatuur te verlagen. Dit geldt ook voor koorts boven de 40 graden. Ook voorkomt paracetamol koortsstuipen niet. Als uw kind pijn heeft, hangerig is of zich ziek voelt, kan paracetamol helpen. Geef paracetamol op vaste tijden volgens de gebruiksaanwijzing. Zie ook de folder 'Pijnstilling bij kinderen'. Het gebruik van paracetamol staat de normale genezing van uw kind niet in de weg.

Antibiotica (op recept van een arts)

Bij sommige infecties kunnen antibiotica nodig zijn. Het is belangrijk om te weten dat behandeling met antibiotica niet helpt tegen virussen. Ook kan het niet altijd bacteriële infecties voorkomen. Of uw kind antibiotica nodig heeft, moet door een arts worden beoordeeld. Wanneer uw kind antibiotica gebruikt, kunnen bijwerkingen optreden, zoals huiduitslag, braken of diarree. Als uw kind bijwerkingen krijgt, neemt u dan contact op met uw huisarts.

Nog vragen?

Mocht u na het lezen van deze folder nog vragen hebben, neemt u dan gerust contact op met uw huisarts of de behandelend arts op de polikliniek.

Meer informatie

Meer informatie vindt u op www.sehzorg.nl/koortskinderen of www.thuisarts.nl/koorts-bij-kinderen. Informatie voor kinderen op: www.kindenziek.nl.

Glastest

Doe de 'glastest' als uw kind ziek is en vlekjes krijgt. Duw een glas stevig tegen de huid. Als de vlekjes zichtbaar blijven door het glas heen, kan dit wijzen op ernstige infectie en is het belangrijk snel medische hulp te vragen.

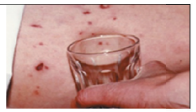

Foto glastest: meningitisnow.org

Koortsstuip

Bij kinderen van drie maanden tot zes jaar kan bij koorts een koortsstuip optreden. Dit is een aanval van trekkingen met armen en benen, waarbij het kind het bewustzijn verliest. Het komt bij 1 op de 20 kinderen voor. Meestal gaat de aanval na enkele minuten vanzelf over. Wanneer uw kind een koortsstuip heeft, is het belangrijk bij uw kind te blijven en te zorgen dat hij of zij zich niet kan bezeren. Bel 112 wanneer de stuip langer duurt dan 5-10 min. Bel anders de huisarts, die u zo nodig verwijst naar een kinderarts. Koortsstuipen veroorzaken geen schade aan de hersenen en bij een gewone koortsstuip is geen aanvullend onderzoek nodig.

Waar moet u op letten bij uw kind? Uw kind heeft koorts en...

- Reageert niet, is erg moeilijk wakker te maken of is verward
- Wordt blauw, bleek of grauw
- Heeft ademstops of een fors kreunende ademhaling
- Is erg benauwd, 'hapt naar adem'
- Heeft een aanval met trekkingen van armen en/of benen die niet stopt

→ **Bel 112**

- Krijgt vlekjes op de huid die niet verdwijnen bij de glastest (zie vorige pagina)
- Is moeilijker wakker te maken
- Wordt binnen enkele uren zieker
- Is ontroostbaar
- Is benauwd of heeft een snelle en/of reutelende ademhaling
- Drinkt veel minder dan normaal
- Plast veel minder dan normaal
- Braakt voortdurend
- Heeft voortdurend diarree
- Heeft pijn bij het plassen
- Heeft koorts die langer duurt dan vijf dagen
- Uw kind is anders dan anders en u maakt zich zorgen

→ **Neem nu contact op met uw (huis)arts**

- Drinkt minder, maar plast regelmatig
- Is hangerig en moe, maar speelt wel
- Heeft geen 'oranje' of 'rode' symptomen zoals hierboven beschreven
- Hoest, maar is niet benauwd
- Huilt meer, is wel te troosten

→ **Volg adviezen in deze folder**

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Supplementary file 5. List of codes and categories

Content area a) and b): Views on, and experiences with managing a child with fever

Theme	Subtheme · Code
Views on fever	Causes of fever · Bacteria or viruses cause fever · Reaction of the body · Infection Fever has a function, but ... · High fever is alarming · Long duration of fever is alarming · Accompanying symptoms alarm Paying extra attention to the child · Changed behaviour is alarming · Drinking must be good · Urinating must be good
Management of a febrile child	Mixed thoughts about paracetamol · Should always be given in case of fever · Only needed when the child suffers · It supresses the function of the fever Methods to lower the temperature · Using paracetamol · Using homeopathic medicine · Undressing the child · Giving a cold shower/cold wipes
Thoughts about antibiotics	Only when really necessary · Fear of resistance of the body · Trust in function of the body · Needed in specific situations · It depends on the doctor
Help-seeking behaviour	Age of child is important · Babies aren't able to express themselves Role of experience · Experience with earlier episodes · Having multiple children · Social network Trust in parental intuition · Taking decisions on intuition Circumstances of fever · Long duration of fever · High fever · Fever in combination with other symptoms Insecurity about timing and options · Child always ill at Fridaynight · When and who to call?

Thoughts about health care	Feeling reassured after consultation · Trust in doctor · I have done everything needed Feeling not to be taken seriously · Doctors don't really listen · Child doesn't get a diagnosis Threshold to seek medical help during out of hours service · Good doctor-patient relationship with GP · Fear of rejection · Child always ill at Fridaynight

Content area c): Information seeking

Theme	Subtheme · Code
Source of searched information	Internet as most common resource to… · Look up the symptoms · Search where to go for medical help · Search when to seek medical help · Read experience from other parents Asking for advice to surroundings · Management of the ill child · Possible diagnosis
Appreciation of searched information	Internet is as easily accessible but not always helpful · Too much information · Too general information · Increases anxiety and concerns · Contains inconsistent information Leaflets are not easy to reread · Not easy to find when really needed
Delivery of needed information	Prefer a doctor · Possibility to ask questions · More personal Internet is easy but confusing · Before calling the doctor Written material with audiovisual support · Reading information most preferred · Videos and pictures for better understanding
Content of needed information	Needing guidance in care for the child · Illness management · Referral to appropriate services · Timing to seek medical attention Needing information about children's illness
Quality criteria of needed information	Reliability of information · Professional endorsement Consistent information Easy accessibility of information

Chapter 5

Summary and general discussion

In this chapter, we will summarize and discuss the main findings of this thesis on decision-making in childhood pneumonia in the ED. In **chapter 5.1**, we will summarize what the knowledge gaps were before this thesis, and what this thesis adds. How these topics fit in care pathway of the paediatric ED is depicted in Figure 1. **Chapter 5.2** will discuss several overarching themes of the thesis in more detail: a) the relevance of studies on practice variability; and b) methodological and practical issues related to the application of prediction models in clinical practice. In **chapter 5.3** we look at future perspectives of diagnostic and treatment decisions for childhood pneumonia in the ED.

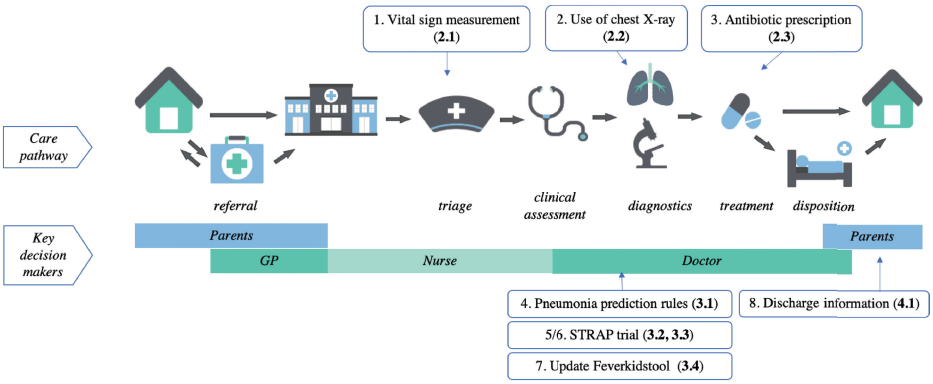

Figure 1. Knowledge gaps and thesis chapters (between brackets) along the care pathway of the paediatric ED

5.1 Summary of main findings

Knowledge gaps before this thesis

Variability in management of childhood pneumonia in the emergency department

A major challenge in the management of children with fever and respiratory tract infections (RTIs) is to identify those with serious bacterial infections that need antibiotic treatment, among the majority with self-limiting illness. The NICE guideline for the assessment of febrile children recommends to look for warning signs for serious illness, including the routine measurement of four vital signs (temperature, heart rate, respiratory rate and capillary refill), but adherence to this recommendation in routine practice is unknown **(gap 1)**. Chest X-rays have limited reliability for this bacterial pneumonia, and current international guidelines recommend against routine use of these X-rays in children with an uncomplicated pneumonia presentation. Little is known about how chest X-rays are currently used in treatment decisions of children with suspected lower RTIs in the ED **(gap 2)**. In the absence of a gold standard for bacterial pneumonia, practice variation in the management of children with fever and RTIs has been described in various settings.[1,2] However, recent data on antibiotic prescription for

children European EDs are lacking, as is insight in the determinants of variability in antibiotic prescription for RTIs **(gap 3)**.

Supporting treatment decisions for childhood pneumonia

Clinical prediction models for childhood pneumonia exist, but none of them is well implemented in clinical practice. It is unclear if these prediction models – that are mostly developed with chest X-ray as their reference standard – can be used to guide antibiotic treatment decisions **(gap 4)**. The Feverkidstool is a clinical prediction model combining clinical characteristics and c-reactive protein (CRP). This model has been validated in different settings, but has not yet been used as a decision rule to guide antibiotic prescription. It is unknown how such a decision rule would impact antibiotic prescription rates in clinical practice, whether this approach would be safe and what the cost implications would be **(gaps 5, 6)**. Next to CRP, new biomarkers have been developed with better diagnostic accuracy for viral versus bacterial infections, for example the ImmunoXpert. This is a host-protein based assay, combining tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma induced protein-10 (IP-10), and CRP. Use of the ImmunoXpert instead of CRP in the Feverkidstool may improve the diagnosis of bacterial infections in children **(gap 7)**.

Supporting parents' decisions for their child with a fever

In the period preceding the ED visit, and after ED discharge, parents are the key decision-makers for their child with fever. Clear discharge information is vital to support parents in managing their sick child at home. For this information to be effective, knowledge about parents' views on fever and their needs for information after the ED visit is crucial, but information on these topics is currently limited **(gap 8)**.

What this thesis adds

In a national and a European population of children visiting the ED we observed large practice variation in the management of children with fever and RTIs. In **chapter 2.1** we showed that most European hospitals have adopted the NICE guideline recommendation to measure vital signs in all febrile children under five, but that adherence to this recommendation in routine practice was only moderate. The frequency of measuring vital signs differed across hospitals, and was higher in younger children, those with RTIs and those with a higher triage acuity level. In **chapter 2.2** we observed that in the Dutch ED setting, in 18% of children with fever and respiratory symptoms a chest X-ray was performed. Regardless of the result of the X-ray, the decision to perform a chest X-ray independently increased the likelihood of antibiotic prescription. In **chapter 2.3** we showed that RTIs are the most common reason of antibiotic prescription in European EDs, due to their high prevalence. Antibiotic prescription was also

most variable for this diagnosis, which could not be explained by patient characteristics, diagnostic workup or hospital characteristics.

In **chapter 3.1** we showed that three out of seven existing clinical prediction models for childhood pneumonia were associated with a consensus diagnosis of bacterial versus viral infection, identifying those children in need for antibiotics. These models could identify children at low risk of bacterial pneumonia, having the potential to guide antibiotic treatment decisions. In **chapter 3.2** we present the results of a stepped wedge cluster randomized trial, where we implemented the Feverkidstool as a decision rule to guide antibiotic prescription in eight EDs in The Netherlands. The decision rule did not reduce overall antibiotic prescription, but was non-inferior to usual care. We observed a reduction of strategy failures and of antibiotic prescriptions in children with a low/intermediate risk for pneumonia, suggesting improved targeting of antibiotics by the decision rule. In addition, **chapter 3.3** shows that use of the decision rule was cost-saving from a healthcare and societal perspective, due to less frequent and shorter hospitalizations, and fewer lost parental workdays. In the **chapter 3.4** we updated the Feverkidstool by replacing CRP with the combination assay ImmunoXpert in a population of children under five with lower RTIs or fever without source, using an expert panel as the reference standard for defining pneumonia and other bacterial infections. This resulted in improved diagnostic accuracy, especially in a subgroup of children with a low/intermediate predicted risk of bacterial infection.

Chapter 4.1 deals with the last step in the chain of care for febrile children in the ED. We developed a hospital discharge information package, based on qualitative data from parents of young children. Parents were concerned about their febrile child either based on specific symptoms of the child or based on an undefined parental intuition. Parents reported improved knowledge about fever and more confidence in caring for a febrile child after consulting the information package.

5.2. General discussion

Variability studies informing policy and future research

It has since long been recognized that studies on variability in care are important to improve quality and resource use in healthcare.[3,4] Even though variability itself does not prove high or low quality of care, observed practice variation can often only partly be explained by differences in population and epidemiology.[3,5] This was confirmed by our variability studies (chapters 2.1 – 2.3), where we evaluated three important aspects of fever management in children: measurement of vital signs, use of chest X-rays and antibiotic prescription. For example, our analysis on antibiotic prescription in Europe (chapter 2.3) showed that even

after extensive adjustments for population and setting characteristics, substantial variability in prescription for RTIs across EDs remained. What can we learn from our variability studies about the management of fever in children in the ED?

First, they provide information on the extent and background of a problem and can thereby guide interventions to improve paediatric emergency care. We collected data prospectively and in a uniform manner, making comparisons across hospitals and countries possible. For all three areas that we studied, we observed that practice variability was driven by patient characteristics and disease severity, but also by setting (hospital or country). However, the potential reasons for this variability, and thereby the clinical implications, may be different. Regarding the measurement of vital signs, the NICE guideline advice was very clear and specific: *'measure temperature, heart rate, respiratory rate and capillary refill in all febrile children under five'*.[6] However, high-quality evidence for the predictive ability of these four vital signs to identify serious illness is lacking.[6,7] Therefore, the observed practice variation may indicate poor implementation of the guideline, *or* that decisions are made to not apply the guideline advice to certain patients. Our results call for further scientific underpinning of this guideline recommendation, and – if sufficient evidence is available – for a better understanding of the reasons for nonadherence. In the case of chest X-ray use in children with suspected lower RTIs, we observed practice variability across eight Dutch EDs. Even though X-ray use was much lower than in studies from the US,[8,9] we discovered that chest X-ray results only played a minor role in the decision to prescribe antibiotics. Thereby our study confirmed the guideline recommendation to not routinely use chest X-ray in non-complex patients. We observed a very low frequency of complicated illness (<1%), further emphasizing the limited added value of chest X-rays in a low risk population as in the paediatric ED. These results can be used to further reduce unnecessary use of chest X-rays for uncomplicated pneumonia in the ED in The Netherlands, and serve as an example for high-utilizing countries. The observed variability in antibiotic prescription for RTIs may have a more complex background. The indications for antibiotic prescription in the guidelines are less clear-cut, as a result of the lacking gold standard for childhood bacterial pneumonia. However, our findings fit in a growing body of evidence on variation in antibiotic use, pointing out that reduction of antibiotic prescription in the paediatric ED is possible.[5,9-15]

Second, variability studies show where most potential gain of an intervention is, in terms of geographical regions or specific patient groups. Countries or hospitals with poor adherence to the NICE recommendation to measure vital signs should find out reasons for nonadherence and improve implementation of this advice. Hospitals that perform most chest X-rays or prescribe most antibiotics should improve their management of febrile children on these

fronts. It has been shown previously that high use of diagnostic tests is associated with more aggressive treatment, also after correction for disease severity of patients.[9] This was confirmed by our finding that the mere performance of chest X-ray increased the likelihood of prescribing antibiotics, and not the result. In addition to specific settings, we could also identify specific patient groups who may gain most of interventions to improve diagnostic testing or treatment. Most benefit in improving vital sign measurement can be expected in patients with a higher prior risk of serious illness, e.g. fever without source.

Efforts to reduce unnecessary antibiotic prescription should target children with RTIs. In the first place because RTIs are the most common reason to prescribe antibiotics in the ED due to their high prevalence. In addition, because antibiotic prescription rates for RTIs showed most variability across hospitals, suggesting most room for improvement.

Third, our studies provide input for the design of intervention studies to improve management of children with fever and RTIs. Baseline antibiotic prescription rates varied across and within European countries, affecting sample size calculations of studies aiming to improve antibiotic prescription. For example, if 500 patients are needed in a trial to show a 10% reduction in antibiotic prescription in The Netherlands by a certain intervention, fewer patients will be needed in a country with a higher baseline prescription rate. The observed variability also emphasizes the importance of performing multi-centre and multi-national studies. This will improve generalizability of findings to the wider European setting and increase standardization of care at the international level. It must be noted that antibiotic prescription in the paediatric ED care still is a small proportion, when compared to prescription in primary care and in adult care.[16-19]

Decision rules in clinical practice

Decision thresholds

When translating a clinical prediction model – that provides a probability of having the outcome – into a decision rule for clinical practice, decision thresholds need to be defined. In case of the STRAP trial (chapter 3.2), the Feverkidstool was translated into a decision rule with a specific threshold below which antibiotics would be withheld. Choosing a decision threshold warrants careful consideration of the potential benefit of the intervention (in our case the reduction of unnecessary antibiotic treatment) versus the potential harm (under treatment of bacterial infections). We chose a threshold of 10%. In the validation cohort of the original publication of the Feverkidstool this threshold provided a sensitivity of 75%, which rule out value was considered sufficient to be a safe threshold, while still having the potential to reduce antibiotic prescription.[20] Figure 2a shows the observed effect of our intervention on antibiotic prescription in a complete case analysis of the STRAP population. We observed a 65% reduction in antibiotic

prescription in the low/intermediate risk children (from 17% [29/172] to 6% [15/234]). At the same time prescriptions increased by 25% in the high-risk children (from 47% [75/159] to 59% [83/140]). This resulted in an overall reduction of 16% in the whole population, which – in the multilevel and adjusted for time analysis described in chapter 3.2 – appeared not to be significant. In our validation study (chapter 3.1) we also explored a threshold of 15% for the Feverkidstool in two populations, which would result in greater benefit, with a minor increase in potential harm. If we applied this threshold to the STRAP pre-intervention population, and assumed the same changes in antibiotic treatment would occur (-65% in low/intermediate risk and +25% in high risk children), 14 extra children would have been managed without antibiotics. This would have resulted in a sharper decline of overall antibiotic prescription: a reduction of 29% instead of 16% (Figure 2b). It is difficult to predict what the consequences of a higher decision threshold would have been on strategy failure. In our trial we observed a reduction in strategy failures (from 23% [131/572] to 16% [61/381]). Using a 15% threshold, 14 extra children would have been discharged without antibiotics. Still, even if we assumed that all these 14 children would have strategy failure, this would not have led to an increase in strategy failure in the whole group (expected change in strategy failure from 23% to 21%). The risk of strategy failure is also safeguarded in the follow-up strategy of children after the ED visit. It has been shown that if children with pneumonia deteriorate clinically, they usually revisit the ED after 48 hours.[21] This relatively slow disease course legitimates a watchful waiting approach, provided that good safety-netting is in place and patients have good access to care. Good safety-netting implies that the patient information is tailored to parents' needs, and includes precise information on how to manage the febrile child at home and when to return to a healthcare professional.[22-24] This is essential to ensure the safety of interventions that change clinical decision-making in young febrile children in the ED.

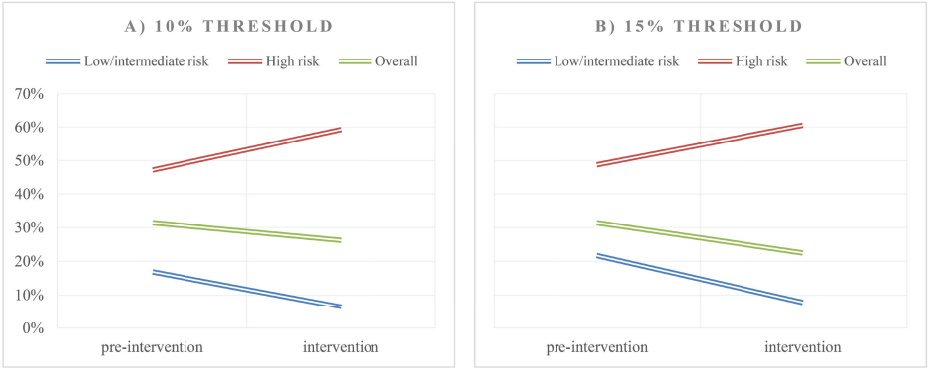

Figure 2. Antibiotic prescription during the pre-intervention period.
A) observed impact of the Feverkidstool at the 10% decision threshold; B) expected impact at 15% threshold.

Presentation of risks

The observed increase in antibiotic prescription in the high-risk population was not expected, and raises another practical issue. When implementing prediction models as decision rules in clinical practice, the question is how to visualize the predicted risk of the individual child to the healthcare provider. In the STRAP trial we chose to provide a qualitative risk classification to the treating physician, instead of the exact percentage: the predicted risk was presented as either 'low (<3%)', 'intermediate (4-10%)' or 'high (>10%)'. Even though it was explicitly stated to perform usual care in children with a high predicted risk, this term 'high risk' may have influenced the clinician and increased prescriptions. However, the exact median predicted risk in the high-risk children that received antibiotics was slightly higher in the intervention group than in the pre-intervention group (29% [IQR 18-43%] versus 21% [IQR 16-43%]). This may indicate that these children had a more severe clinical presentation, and may partly justify the increase in antibiotic prescription during the intervention period.

Evaluation of impact: more than effectiveness

The evaluation of a decision rules in clinical practice includes more than studying the change in clinical outcome. Interventions in healthcare are usually complex in nature and have an impact on multiple aspects of the health system.[25-28] These can include costs, process outcomes (for example length of stay) or patient-reported outcomes. These system-wide effects are especially important when deciding to scale up an intervention to the national or international level. In the case of the Feverkidstool, we showed that the decision rule was cost-saving for the most important cost drivers of children with RTIs: hospitalization and parental absenteeism. The main cost drivers and the high prevalence of RTIs are similar in other European settings, so the decision rule is likely to have a cost benefit in other settings as well. Regarding the improving of antibiotic prescriptions, the underlying goal is to prevent antimicrobial resistance. Even though this could not be captured in our study, it remains an important outcome that should be considered in the evaluation of decision rules supporting antibiotic treatment decisions.

The role of biomarkers in the management of fever and RTIs

CRP-testing in febrile children: yes or no?

In current clinical practice CRP is the only routinely available, easy to perform and affordable point-of-care biomarker in the ED setting.[29] The association between CRP and bacterial pneumonia has been well described in studies in children as well as in adults.[30-35] It has a good rule-in value at a threshold of >100mg/L, but a moderate rule-out value even at a low threshold.[31] The use of CRP testing in the routine assessment of febrile children in the ED is an issue of ongoing debate. Recently, some authors have argued to test CRP in all febrile

children already at the moment of triage [36], but others raised questions on the feasibility and validity of such approach.[37] The Feverkidstool does include CRP, so implementation of the tool in routine practice required a capillary blood sample in all children with fever and respiratory complaints. What can we learn from this thesis on how to balance clinical assessment and biomarkers in the management of the febrile child in the ED?

CRP during the STRAP trial

During the conduct of the STRAP trial we encountered that many paediatricians preferred not to measure CRP routinely in all children meeting the inclusion criteria, even though in the Feverkidstool CRP was combined with clinical characteristics. It has been described that more diagnostic testing is associated with more aggressive treatment of children in the ED.[9] Physicians in the STRAP trial were most concerned about false-positive tests (and overuse of antibiotics) in children with viral infections, false reassurance by low CRP-values in early stage disease, uncertain aetiology and thereby overtreatment of children in the 'grey area' of intermediate CRP-levels (between 20-80 mg/L). They stated that clinical assessment of the doctor should be leading in treatment decisions, not a CRP-value (unpublished qualitative data). The majority of included children in our trial (54%) had a CRP-value below 20 mg/L. In 10% of cases CRP was >80 mg/L, and 36% were in the intermediate, grey area (Table 1). This distribution is comparable to other cohorts of febrile children in the ED that have been described.[20,36,38] We observed that across all CRP-categories, antibiotic prescription slightly decreased during the intervention period, suggesting that the combination of CRP with clinical findings in the Feverkidstool was beneficial. In addition, when we looked at antibiotic prescription across hospitals with varying levels of CRP-testing in the pre-intervention period, we found no evidence for increased antibiotic prescription in hospitals that started to test CRP more often in the intervention period (Figure 3). A notable finding was that in both phases of the trial, some children with presumed viral infections still received antibiotics (e.g. 22/196, 11% of all children diagnosed with bronchiolitis). Introduction of the Feverkidstool, including CRP measurement, did not influence prescriptions in these children. Based on our findings and the available literature, we conclude that CRP should be interpreted together with clinical signs and symptoms for optimal diagnostic accuracy in children with suspected lower RTIs.[39-42] In this way CRP does not increase unnecessary antibiotic prescriptions, and can safely be used to guide treatment decisions.

Table 1. Antibiotic prescription by CRP categories

	Overall	Pre-intervention	Intervention
CRP categories			
CRP <20	51/404 (13%)	30/195 (15%)	21/209 (10%)
CRP 20 - 80	99/270 (37%)	52/136 (38%)	47/134 (35%)
CRP >80	70/80 (88%)	39/43 (91%)	31/37 (83%)

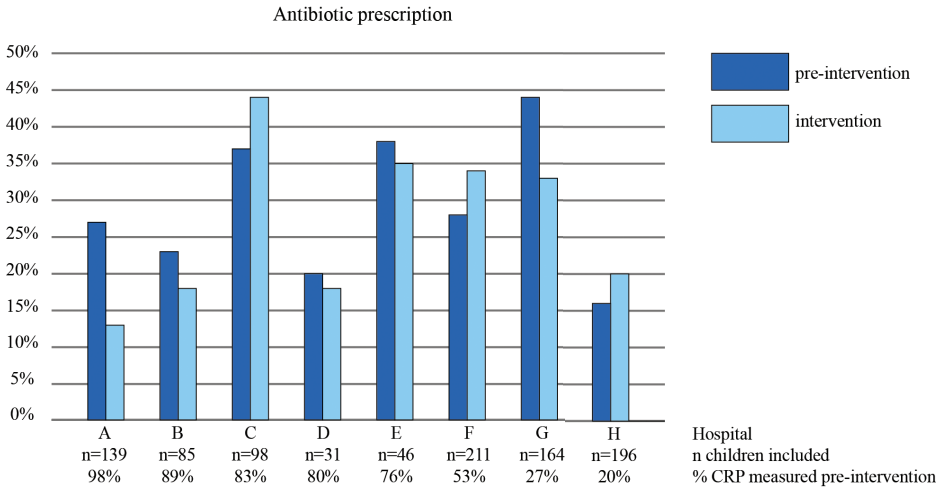

Figure 3. Antibiotic prescription rates (%) in hospitals with varying levels of CRP-testing in pre-intervention care
Legend: A-H = hospitals; n=total included children; %CRP= percentage of children in whom CRP was measured in the pre-intervention period. In the intervention period in >90% of children CRP was tested in all hospitals.

Improving diagnosis by new biomarkers?

Even though CRP and clinical judgment should be combined for optimal diagnostic accuracy, they are still imperfect diagnostics for bacterial infection and some diagnostic uncertainty remains. More accurate biomarkers are being developed to reduce this diagnostic uncertainty of bacterial versus viral infections in children.[38,43] How can they be added to the diagnostic pathway in routine care? In chapter 3.4 we observed that the diagnostic accuracy of the Feverkidstool increased when we updated the tool by replacing CRP with a host-protein based assay (the ImmunoXpert) that combines bacterial and viral biomarkers. We found most added value of the updated Feverkidstool in the group of children with low to moderate predicted risk by the original Feverkidstool. This points out that a combination of clinical findings and CRP may identify a subgroup of children that will benefit from new, more accurate biomarkers.

5.3. Future perspectives

Pneumonia reference standard for diagnostic research

As mentioned frequently throughout this thesis, no gold standard exists for childhood pneumonia. This hampers the proper judgment of the accuracy of diagnostic tests and of the appropriateness of antibiotic use. In this thesis, we have used different approaches to handle this problem: in our validation study of prediction models for childhood pneumonia (chapter 3.1) we used a predefined algorithm, based on available clinical information to define bacterial pneumonia.[44] In our update of the Feverkidstool with the ImmunoXpert (chapter 3.4) we used an expert panel diagnosis as a reference standard.[45] In the STRAP trial (chapter 3.2), we did not define a reference standard for bacterial pneumonia, but focused on consequences of the diagnosis (need for antibiotics, strategy failure) instead of the diagnosis itself.[28] Consensus about the optimal reference standard for bacterial pneumonia in children is urgently needed. A prospective study comparing the different approaches would be useful to judge the different pros and cons, to come to a consensus and to interpret existing studies on childhood pneumonia.

Improving treatment decisions for childhood pneumonia

Appreciating the results of the Feverkidstool so far, next steps would be to evaluate the impact of the Feverkidstool in high-prescribing settings, in settings with a low prevalence of bacterial infections, or using a higher decision threshold. Another future perspective for the Feverkidstool is to use this model to position new diagnostic tests for childhood pneumonia. New biomarkers are being developed, raising questions about their use in research and clinical practice: how accurate are the new biomarkers, who should be tested, how can they guide treatment, what is the availability and affordability of the tests? As we have shown in the update study of the Feverkidstool with ImmunoXpert, the benefit of this new biomarker was found in a subgroup of patients. Such a hierarchical approach should be developed for diagnosing pneumonia, in order to make the most accurate diagnosis, without overuse of expensive and scarce resources. It should start with readily available and cheap diagnostics (like clinical assessment and CRP) and save the more advanced testing for patients in whom diagnostic uncertainty remains.

Outcomes in paediatric emergency care

In the STRAP trial we focused on the impact of the Feverkidstool on antibiotic prescription, safety and costs. These are important clinical outcomes, but also other factors should be explored. Patient reported outcome measures (PROM) are widely used in current research and clinical practice. For example, a recent study showed that parents of febrile children in the

ED care most about reducing visit times, avoiding painful procedures and getting diagnostic information faster.[46] In the development or evaluation of new interventions, such outcomes should be taken into account.

Improving decision support for parents

In our qualitative study we developed a discharge information package for parents, including videos on how to recognize signs of severe illness, for example nasal flaring or retractions. However, a recent publication showed that there is a large discrepancy in the assessment of disease severity in children with RTIs between parents and physicians.[47] Parents focused more on behavioural symptoms like 'change in cry', 'disturbed sleep' or 'reduced eating', while physicians relied almost exclusively on physical examination. This discrepancy has consequences for the way we provide discharge instructions after the ED, but also how we value the history the parents tell. Future research should evaluate the predictive value of behavioural symptoms that parents use to judge disease severity, and discharge information should be tailored accordingly.

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Hoofdstuk 6.

Nederlandse samenvatting

Inleiding

Koorts en luchtweginfecties komen heel vaak voor bij kinderen en zijn de belangrijkste reden waarom kinderen naar de huisarts of de spoedeisende hulp (SEH) worden gebracht. Luchtweginfecties geven klachten zoals koorts, hoesten en benauwdheid. Meestal worden ze veroorzaakt door virussen en gaan vanzelf over. Echter, soms heeft een kind een longontsteking door een bacterie, die ernstig kan verlopen en met antibiotica moet worden behandeld. Antibiotica werken niet tegen virusinfecties. Het verschil tussen een virusinfectie of een infectie door een bacterie is soms moeilijk te maken. De klachten lijken erg op elkaar, en er zijn geen perfecte testen om dit verschil aan te tonen. Bloedtesten en longfoto's zijn wel beschikbaar, maar die zijn niet 100% betrouwbaar voor het aantonen van een bacteriële longontsteking. Het is belangrijk om niet onnodig antibiotica te gebruiken, want dat draagt bij aan resistentie van bacteriën. Dat wil zeggen dat bacteriën ongevoelig worden voor antibiotica, waardoor het moeilijker wordt om ze te bestrijden. In de praktijk beslist de arts bij een kind met koorts en luchtwegklachten of hij/zij antibiotica nodig heeft op basis van een combinatie van symptomen, lichamelijk onderzoek en aanvullende testen. In dit proefschrift onderzoeken we of de beslissingen over diagnose en behandeling kunnen verbeteren bij kinderen die met koorts en luchtweginfecties op de SEH komen.

Variatie in de behandeling van kinderen met koorts en luchtweginfecties

Een internationale richtlijn (de NICE-richtlijn voor de behandeling van kinderen met koorts) adviseert om bij alle kinderen met koorts onder de vijf jaar standaard vier vitale parameters te meten: temperatuur, hartslag, ademhalingssnelheid en capillaire refill (maat van doorbloeding). In **hoofdstuk 2.1** hebben we onderzocht hoe goed dit advies werd opgevolgd in de praktijk. We hebben hiervoor data gebruikt van meer dan 5000 kinderen met koorts die de SEH bezochten van 28 ziekenhuizen in 11 verschillende Europese landen. We constateerden dat het advies matig werd opgevolgd: bij minder dan de helft van de kinderen onder de vijf jaar waren alle vier parameters gemeten en geregistreerd. Er waren grote verschillen tussen ziekenhuizen en de metingen waren vaker compleet bij jonge kinderen, kinderen met luchtweginfecties en bij kinderen met urgent ziektebeeld (waarvoor snelle beoordeling nodig is).

De longfoto is lange tijd gezien als beste test om een longontsteking aan te tonen. Tegenwoordig is veel bekend over de beperkingen van deze test. Ten eerste, wanneer meerdere beoordelaars naar dezelfde foto kijken, komen ze vaak tot een verschillende uitslag. Ten tweede is het niet te zien of de afwijkingen op de foto door een virus of een bacterie worden veroorzaakt. Daarom adviseren internationale en Nederlandse richtlijnen om niet bij alle kinderen met luchtwegklachten een foto te maken, maar alleen bij kinderen met een

gecompliceerd ziektebeloop. **Hoofdstuk 2.2** beschrijft hoe vaak tegenwoordig een longfoto wordt gemaakt bij jonge kinderen die met luchtwegklachten op de SEH komen, en of die foto invloed heeft op beslissing om antibiotica voor te schrijven. Bij een groep van bijna 600 kinderen onder de vijf jaar uit acht Nederlandse ziekenhuizen stelden we vast dat een op de vijf kinderen een longfoto krijgt, terwijl geen van hen een gecompliceerd beloop had. Het maken van deze foto – ongeacht de uitslag ervan – leidde tot het vaker voorschrijven van antibiotica. Dit laat zien dat de longfoto weinig toegevoegde waarde heeft in het maken van de beslissing om wel of geen antibiotica voor te schrijven. Daarmee bevestigt ons onderzoek het advies van de richtlijn om niet standaard een longfoto te maken bij kinderen met een ongecompliceerde luchtweginfectie.

In de literatuur is regelmatig beschreven dat er grote verschillen zijn in het voorschrijven van antibiotica. Er was alleen geen recent onderzoek naar verschillen in antibioticavoorschrift bij kinderen op de SEH in Europa. Ook was niet bekend waardoor eventuele verschillen verklaard kunnen worden. In **hoofdstuk 2.3** hebben we dit onderzocht, in dezelfde groep kinderen als hoofdstuk 2.1. We zagen dat de meeste antibiotica werden voorgeschreven voor luchtweginfecties, omdat die het vaakst van alle infecties voorkomen. Binnen deze groep van kinderen met luchtweginfecties waren grote verschillen te zien in antibioticavoorschrift tussen de 28 ziekenhuizen. Er waren dus ziekenhuizen waarbij de dokters relatief weinig antibiotica voorschreven en ziekenhuizen waar veel meer antibiotica werd gegeven. Deze verschillen konden niet worden verklaard door het feit dat kinderen in het ene ziekenhuis ernstiger ziek waren dan in het andere ziekenhuis. Deze bevinding wijst op overbehandeling met antibiotica, en geeft dus aan dat antibioticavoorschrift verminderd kan worden.

Ondersteuning van behandelbeslissingen voor longontsteking bij kinderen

De beslissing van de arts om wel of geen antibiotica te geven, kan op verschillende manieren worden ondersteund. Zoals genoemd zijn er diverse richtlijnen beschikbaar voor de behandeling van koorts en longontsteking bij kinderen. Hoewel richtlijnen zeer nuttig en nodig zijn, zijn ze niet altijd gebaseerd op hoogstaand bewijs, zijn de adviezen vaak algemeen en niet altijd toepasbaar op de individuele patiënt. Een andere vorm van beslisondersteuning kan worden gegeven door beslisregels. Beslisregels zijn gebaseerd op voorspelmodellen die aan de hand van strikte methodologische stappen zijn ontwikkeld. Deze voorspelmodellen geven een precieze uitslag voor de individuele patiënt, bijvoorbeeld de kans (%) dat een kind een bepaalde ziekte heeft.

In **hoofdstuk 3.1** hebben we de literatuur doorzocht om te kijken welke modellen er zijn om de kans op een bacteriële longontsteking bij kinderen te voorspellen. Ook hebben we

onderzocht of deze modellen gebruikt zouden kunnen worden om de beslissing wel/geen antibiotica te verbeteren. We vonden in de literatuur zeven voorspelmodellen voor een bacteriële longontsteking, maar die werden nog niet in de praktijk toegepast. Drie van de zeven konden het risico op een bacteriële longontsteking goed voorspellen. Omdat deze drie voorspelmodellen een groep kinderen met een laag risico konden identificeren, zouden ze gebruikt kunnen worden om de behandelbeslissing van de arts te sturen.

Een van de voorspelmodellen die we vonden is de Feverkidstool. Dit is een voorspelmodel dat aan de hand van klinische gegevens (zoals leeftijd, hartslag en ademhalingssnelheid) en een ontstekingswaarde (CRP) het risico op een longontsteking kan voorspellen. Dit model is al uitgebreid gevalideerd in verschillend groepen patiënten, maar nog niet in de praktijk gebruikt als ondersteuning van de behandelbeslissing. **Hoofdstuk 3.2** beschrijft de resultaten van een grote studie (de STRAP-studie), waarin de Feverkidstool als beslisregel is gebruikt om het voorschrijven van antibiotica te sturen. Het advies was daarbij dat alle kinderen met een laag of gemiddeld risico op een bacteriële longontsteking (<10%) geen antibiotica zouden krijgen. We hebben daarvoor een stepped-wedge design gebruikt, waarbij acht Nederlandse ziekenhuizen één voor één overgingen van 'gewone zorg' naar 'antibioticavoorschrift volgens de beslisregel Feverkidstool'. We stelden vast dat de beslisregel het algehele antibioticavoorschrift tijdens het onderzoek niet heeft verlaagd. Wel zagen we dat er minder therapie-falen was, en dat aan de kinderen met een laag/gemiddeld risico minder antibiotica werd voorgeschreven. Dit wijst op een betere, meer doelgerichte behandeling met antibiotica van de kinderen in de studie. In **hoofdstuk 3.3** vonden we ook dat de invoering van de beslisregel leidde tot een kostenbesparing, doordat er minder ziekenhuisopnames waren en ouders minder werkverzuim hadden tijdens de ziekte van hun kind.

In **hoofdstuk 3.4** onderzochten we of de voorspellingen van de Feverkidstool verder verbeterd konden worden als we een nieuwe bloedtest daaraan toevoegden: de ImmunoXpert. Deze bloedtest combineert de ontstekingswaarde CRP – die ook in de Feverkidstool zat – met twee andere eiwitten: tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) en interferon gamma induced protein-10 (IP-10). We keken of de ge-update Feverkidstool (met ImmunoXpert in plaats van alleen CRP) beter kon voorspellen of een kind een bacteriële infectie had. Deze bacteriële infecties werden vastgesteld door een panel van drie experts. In een groep van bijna 600 Nederlandse en Israëlische kinderen met koorts zonder focus en kinderen met lage luchtweginfecties vonden we dat de ge-update Feverkidstool inderdaad meer accuraat een bacteriële infectie kon voorspellen, met name in de groep kinderen met een laag/gemiddeld risico.

Ondersteunen van beslissingen door ouders voor hun kind met koorts

Zowel voor als na het bezoek aan de SEH, zijn ouders degene die de belangrijkste beslissingen maken in het zorgen voor hun kind met koorts. Daarbij is het belangrijk dat ze goede informatie krijgen over wat ze moeten doen in de thuissituatie, zodra ze ontslagen worden vanaf de SEH. Deze informatie moet goed aansluiten bij de beleving en verwachtingen van de ouders. In **hoofdstuk 4.1** onderzochten we die verwachtingen en informatiebehoefte door middel van een kwalitatief onderzoek onder ouders. Ouders gaven aan vaak bezorgd te zijn om hun kind vanwege specifieke symptomen, maar vaak ook op basis van een onbestemde intuïtie. Als zij zich hierin niet serieus genomen voelden door behandelaren, verhoogde dat de drempel om een volgende keer hulp te zoeken. We ontwikkelden een informatiepakket over koorts bij kinderen, bestaand uit een website met video's, en een folder. Ouders gaven aan meer kennis over koorts en meer vertrouwen te hebben in het zorgen voor een kind met koorts, nadat ze het informatiepakket hadden geraadpleegd.

Appendices

I. Authors and affiliations

II. List of publications

III. About the author

IV. PhD portfolio

V. Dankwoord

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REPEM group (Research in European Pediatric Emergency Medicine)

Appendix II. List of publications

In this thesis:

JS van de Maat, D Peeters, D Nieboer, AM van Wermeskerken, FJ Smit, JG Noordzij, G Tramper-Stranders, GJA Driessen, CC Obihara, J Punt, J van der Lei, S Polinder, HA Moll, R Oostenbrink. Evaluation of a clinical decision rule to guide antibiotic prescription in children suspected of lower respiratory tract infections in The Netherlands: a stepped wedge, cluster randomized trial. *PLoS Med 2020 17(1): e1003034*

JS van de Maat, M van der Ven, G Driessen, A van Wermeskerken, F Smit, J Noordzij, G Tramper-Stranders, C Obihara, J Punt, HA Moll, S Polinder, R Oostenbrink. Cost study of a cluster randomized trial on a clinical decision rule guiding antibiotic treatment in children with suspected lower respiratory tract infections in the emergency department. *The Pediatric Infectious Disease Journal (accepted for publication)*

JS van de Maat, H Jonkman, E van de Voort, S Mintegi, A Gervaix, S Bressan, HA Moll, R Oostenbrink. Measuring vital signs in febrile children at the emergency department. An observational study on adherence to the NICE recommendations in Europe. *Eur J Pediatr 2020; 179, 1097–1106*.

JS van de Maat, D Garcia Perez, GJA Driessen, A van Wermeskerken, F Smit, J Noordzij, G Tramper-Stranders, CC Obihara, J Punt, HA Moll, R Oostenbrink. The influence of chest X-ray results on antibiotic prescription for childhood pneumonia in the emergency department. *(submitted)*

JS van de Maat, E van der Voort, Santiago Mintegi, A Gervaix, D Nieboer, HA Moll, R Oostenbrink, REPEM group. Antibiotic prescription for febrile children at European emergency departments: an observational study. *Lancet Infect Dis 2019; 19: 382-91*

JS van de Maat, D Nieboer, M Thompson, M Lakhanpaul, HA Moll, R Oostenbrink. Can prediction models assess antibiotic need in childhood pneumonia? A validation study in paediatric emergency care. *PLoS ONE 2019; 14(6): e0217570*

CB van Houten, **JS van de Maat**, C Naaktgeboren, L Bont, R Oostenbrink. Update of a clinical prediction model for serious bacterial infections in preschool children by adding a host-protein based assay: a diagnostic study. *BMJ Paediatrics Open 2019;3:e000416*

JS van de Maat, D van Klink, A den Hartogh-Griffioen, E Schmidt-Cnossen, H Rippen, A Hoek, S Neill, M Lakhanpaul, HA Moll, R Oostenbrink. Development and evaluation of a hospital discharge information package to empower parents in caring for a child with fever. *BMJ Open 2018;8:e021697*

Other publications:

JS van de Maat, O de Santis, L Luwanda, R Tan, K Keitel, Primary care case management of febrile children: insights from the ePOCT routine care cohort in Dar es Salaam, Tanzania. *(submitted)*

D Kuijpers, D Peeters, N Boom, **JS van de Maat**, R Oostenbrink, G Driessen. Parental assessment of disease severity in febrile children under 5 years of age: a qualitative study. *(submitted)*

Z Karami, B Knoop, T Dofferhoff, M Blaauw, N Janssen, M van Apeldoorn, A Kerckhoffs, **JS van de Maat**, J Hoogerwerf, J ten Oever. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID- 19. *(submitted)*

NR Pouw, **JS van de Maat**, CM Veerman, J Ten Oever, NAF Janssen, EJ Abbink, MHE Reijers, Q de Mast, W Hoefsloot, R van Crevel, K Slieker, MJ van Apeldoorn, M Blaauw, ASM Dofferhoff, JJ Hoogerwerf. Clinical characteristics and outcomes of 952 hospitalized COVID-19 patients in The Netherlands. *(submitted)*

JS van de Maat, H Waanders, 'Een vrouw met een geinfecteerde pink' Diagnose in beeld: ecthyma contagiosum. *Ned Tijdschr Geneeskd. 2014;158:A7812*

JS van de Maat, NM van der Lugt, IL van Kamp, EAM Knoppert-van der Klein; JGFM Hovens, FJ Walther. Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies. *Early Hum Dev. 2012 Jun;88(6):375-8*

Appendix III. About the author

Josephine van de Maat was born on August 18th 1986 in Almelo, The Netherlands. She grew up in Rijssen, and attended her secondary school at the Jacobus Fruytier Scholengemeenschap in Rijssen and Apeldoorn. In 2004, she started medical school at Leiden University, where she graduated cum laude in 2012. In the meantime, she took several extra-curricular courses at the Faculty of Humanities of Leiden University, including a minor in Latin American studies. During her studies, she was also an active member of the Christian student union C.S.F.R. Panoplia, where she was a board member in the year 2008-2009. Josephine did her master thesis under supervision of prof. dr. Frans Walther at the department of neonatology of the Leiden University Medical Centre (LUMC), studying the outcomes of lithium-exposed pregnancies, which raised her interest in science.

After graduating, Josephine started to work as a clinician on the department of Internal Medicine of the Bronovo Hospital in The Hague. After one year, she moved to the Langeland Hospital in Zoetermeer, where she worked as a doctor on the Emergency Department and Intensive Care Unit. In 2015, she decided to follow her passion for tropical medicine, passed the Netherlands Course in Tropical medicine (NTC) at the Royal Tropical Institute (KIT) in Amsterdam, and worked for three months in Ekwendeni Mission Hospital in Malawi. On her return, she started working in the paediatric intensive care unit in the LUMC, and successfully applied for her PhD research in the Erasmus MC – Sophia Children's Hospital in Rotterdam. In 2016, Josephine started her PhD project under the supervision of prof. dr. Henriette Moll (promotor) and dr. Rianne Oostenbrink (co-promotor) at the department of general paediatrics. The general aim of this research was to improve clinical decision-support in the paediatric emergency department. The main project of this PhD research was the multicentre Study To Reduce Antibiotic Prescription in childhood Pneumonia (STRAP). This trial was performed in close collaboration with eight hospitals in The Netherlands.

During her PhD research Josephine obtained a master degree in Clinical Epidemiology (Netherlands Institute of Health Sciences, Rotterdam) and a master degree in International Health (KIT, Amsterdam). For her master in International Health she studied triage of children in the primary care setting in Tanzania, under supervision of dr. Kristina Keitel from the Swiss institute for Tropical medicine and Public Health. During the last years of her PhD, Josephine followed the PhD curriculum of TULIPS (Training Upcoming Leaders In Paediatric Science). In 2020, Josephine started working as a postdoctoral researcher at the department of infectious diseases and global health at the Radboudumc (Nijmegen), under the supervision of prof. dr. Reinout van Crevel, where she combines her experience in and passion for research, infectious diseases and global health.In her spare time, Josephine likes to travel, cycle, read literature and spend time with her husband, family and friends. In 2017, she married Peter van Grootheest, with whom she lives in Utrecht.

Appendix IV. PhD portfolio Josephine van de Maat

Research school	Netherlands Institute of Health Sciences (NIHES)
Promotor	Prof. dr. H.A. Moll
Co-promotor	Dr. R. Oostenbrink
Department	General Paediatrics

General academic skills	Year	ECTS
Systematic literature retrieval and Endnote	2016	1
Scientific integrity	2016	0.3
Photoshop and Illustrator	2016	0.3
BROK course ('Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers', certified according to Good Clinical Practice guidelines)	2016	1
CPO course: Patient Oriented Research	2016	0.3
Biomedical English writing and communication	2017 – 2018	3
Basic course on 'R'	2018	1.8
TULIPS PhD curriculum	2018 – 2020	4

Research skills	Year	ECTS
Master in clinical epidemiology (NIHES)	2016 – 2019	40
Core courses		
Principles of Research in Medicine & Epidemiology		
Study design		
Biostatistical Methods I: Basic Principles		
Biostatistical Methods II: Classical Regression Models		
Methods of Public Health Research		
Clinical Trials		
Health Economics		
The Practice of Epidemiologic Analysis		
Clinical Translation of Epidemiology		
Clinical Epidemiology		
Principles of Causal Inference		
Repeated Measurements		
Elective courses		
Methods of Clinical Research		
Logistic Regression		
Markers and Prediction Research		
Advanced Analysis of Prognosis Studies		
Qualitative Research Methods for Global Public Health (University of Bergen, Norway)		

Seminars and workshops	Year	ECTS
PhD Day Erasmus MC – Sophia	2016 – 2019	1.5
Young Investigators Day (TULIPS)	2017, 2018	1

National congress presentations	Year	ECTS
Sophia Research Day (oral presentation)	2017, 2018	1.8
Dutch Society for Pediatrics (NVK) (oral presentations)	2017 – 2019	2.7
The Netherlands Society for Tropical Medicine and International Health (NVTG) (poster presentation)	2017	0.9

International conferences	Year	ECTS
Paediatric Resuscitation and Emergency Medicine (PREM), Gent (oral presentations)	2017, 2019	1.8
European Society of Emergency Medicine (EUSEM), Athens (oral presentation)	2017	0.9
European Academy of Paediatric Societies (EAPS), Paris (oral presentation)	2018	0.9
European Society for Paediatric Infectious Diseases (ESPID), Ljubljana (oral presentation), Malmö (poster presentation)	2018, 2019	1.7

Supervising master students	Year	ECTS
D. van Klink, master student Medicine	2016	1.5
A. Griffioen, master-student Medicine	2017	1.5
D. Garcia Perez, master-student Medicine	2017	1.5
H. Jonkman, master student Healthcare management	2018	1.5
L. van Esch, master student Medicine	2018	1.5

Appendix V. Dankwoord

'It takes a village to raise a child'. Dit Afrikaanse spreekwoord geeft aan hoeveel er nodig is om een kind een kans op een gezonde toekomst te geven. Dat principe geldt zeker ook voor de totstandkoming van dit proefschrift. Ontzetten veel mensen hebben bijgedragen aan dit 'boekje', en die wil ik graag bedanken.

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