CHILDREN WITH RESPIRATORY TRACT INFECTIONS:

optimizing point-of-care diagnosis and management in primary care

Marjolein Schot

Children with respiratory tract infections: optimizing point-of-care diagnosis and management in primary care

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Children with respiratory tract infections: optimizing point-of-care diagnosis and management in primary care

Kinderen met luchtweginfecties:
Optimalisatie van diagnose en management in de eerste lijn
(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

General introduction

RESPIRATORY TRACT INFECTIONS IN CHILDREN

Acute respiratory tract infections (RTI) are common illnesses among children (1,2). On average children under twelve years have four to eleven episodes of RTI annually (3). Only a fraction of the children present to the general practitioner (GP), but RTI is still the most common reason children consult a GP (4–6). RTI can be divided in upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI). LRTI can be further divided into acute bronchitis, bronchiolitis and pneumonia. Even though the diagnostic distinction between URTI and LRTI is often made, recent evidence suggests great overlap in these two areas, as described in the unified airway model (7). Reported incidences of RTI in primary care vary, but URTI is much more common than LRTI. In the Netherlands an annual incidence of URTI in children of 94.8 per 1000 was reported, whereas acute bronchitis and pneumonia had an annual incidence of 26.6 and 7.7 per 1000 children respectively (5). These incidences are based on diagnostic labeling by GPs, and most often not verified by additional testing. It is known that this diagnostic labeling can be influenced by factors such as prescribing habits, with GPs labeling a disease to match their prescription decision (8,9).

IMPACT OF RTI

RTI are most often self-limiting, with low risk of complications (10), and also in children with LRTI the disease course is usually mild (11–13). Studies have shown that after two weeks, approximately 80% of children with RTI will be recovered, though duration of cough may be prolonged (14). However, RTI has impact on the general wellbeing of a child and can have impact on the parents and the rest of the family. The disease burden of RTI includes different aspects varying from parental anxiety, missed days at childcare or school, and work absenteeism for parents. Disturbed sleep is reported by 72% of parents with children with acute cough (15). Studies show that parents consulting a GP with their child with RTI are mostly worried about specific symptoms or the duration of symptoms, and expect reassurance from the GP (16,17). Given the high prevalence, RTI in children leads to substantial societal- and economic impact.

DIAGNOSTIC UNCERTAINTY IN SUSPECTED LRTI

Bronchiolitis is assumed to be of viral origin, most often caused by respiratory syncytial virus followed by human rhinovirus (18). Therapy for bronchiolitis is supportive, and given its viral background, antibiotic treatment is not recommended (11,13,18). Although pneumonia can be caused by bacteria, it is also most commonly caused by a viral infection in children. Most research toward the etiology of community acquired pneumonia is done in secondary care. Identification of the causative organism of pneumonia in children is difficult as collection of sputum for analysis is challenging, serological responses are poor in children under 1 year of age and urinary antigen detection tests are unreliable. A large number of studies have been conducted with the aim to

identify the causative pathogen for pneumonia. In 20-60% of pneumonia cases in these studies, the causative organism could not be identified (19). A prospective study in the UK among children admitted to hospital with community acquired pneumonia found that viral infection accounted for 71% of pneumonias (20), whereas a Finnish study found a viral cause in 62% of children hospitalized with pneumonia (21). Combined infections with bacteria and viruses also occur (22). When a bacterial cause for pneumonia is identified, this was most often found to be Streptococcus pneumoniae (19). In general practice, even though pneumonia most often has a viral origin, the identification of a child with pneumonia is essential, as bacterial pneumonia is a serious and potentially life-threatening illness. Even in high income countries such as the UK and USA, lower respiratory tract infection is estimated to cause around 34 deaths per 100 000 children per year and cost 173 000 disability-adjusted life-years per year in children younger than 5 years (23).

For a GP, adequate identification of pneumonia in the ambulant setting is difficult. In evaluating LRTI GPs still mainly rely on history taking and clinical examination for diagnosis and management decisions. Adequate diagnosis and treatment of LRTI is complex, because clinical features do not differ between pneumonia caused by a virus to those caused by bacteria. A systematic review on the diagnostic value of signs and symptoms to identify a child with a serious infection, including pneumonia, found several red flags for serious infection (24). In a setting with low prevalence of serious infection, such as primary care, both parental concern and the clinicians' gut feeling that something is wrong were found to be important red flags. Respiratory rate was the most reliable clinical sign, but the commonly assessed auscultatory signs have low diagnostic value for pneumonia. Pneumonia was very unlikely if a child was not short of breath and there was no parental concern. However, this review was based on 30 studies, of which only one was conducted in primary care. Another large systematic review on the diagnostic value of history and physical examination in the diagnosis of pneumonia revealed similar results (25). Authors reported that no clinical item had sufficient diagnostic value to diagnose pneumonia, and that hypoxia and increased work of breathing (grunting, flaring, and retractions) are more important in the assessment than auscultation. However, hypoxia is a rare finding in primary care.

To add to the complexity of treatment decisions; not all bacterial LRTI require treatment with antibiotics and serious viral infections like viral pneumonia carry a risk for secondary bacterial infection. Thus, awaiting further evidence, clinical guidelines advise to prescribe antibiotics in case of LRTI with an elevated risk for complications and for those with a prolonged course (10,26).

ANTIBIOTIC PRESCRIBING IN CHILDREN WITH LRTI

Medical professionals consider children as a vulnerable group (27) and, given the diagnostic uncertainty in identifying children with a potentially serious bacterial infection, they tend to

overprescribe antibiotics in children with LRTI (28). A systematic review of qualitative studies examined views of clinicians on prescribing decisions in children (29). Clinicians reported to prescribe antibiotics to children with acute infections 'just in case' when they were not confident about the diagnosis or about possible social, health or legal consequences of not prescribing. Doubts about whether parents could safely monitor the illness, especially when patients were not familiar to the physician, was also reported to drive the prescription of antibiotics. Consequently, over-prescription of antibiotics is common (30–32).

Even in a low prescribing country like the Netherlands, 48-63% of antibiotic prescriptions for RTI in children are thought to be non-compliant with guidelines (31,33). This is harmful as antibiotics cause side effects (34), increase re-consultation rates (35) and contribute to antimicrobial resistance. Repeated use of antibiotics increases antimicrobial resistance in communities, but also in individuals (36,37) making it important to correctly identify children who need antibiotics, but equally important to protect those who will not benefit.

POINT OF CARE C-REACTIVE PROTEIN TO IMPROVE THE DIAGNOSIS OF PNEUMONIA?

Biomarkers may support the adequate identification of seriously ill children in general practice. A systematic review that evaluated the diagnostic value of laboratory tests in identifying serious infections in febrile children found that the biomarkers procalcitonin and C-reactive protein (CRP) have value in both ruling in, and ruling out serious infection in secondary care (38). With developing technology, access to additional diagnostic tests in ambulatory settings is increasing, with tests also becoming available as point-of-care tests. For example, point-of-care CRP measurement is increasingly available.

C-reactive protein (CRP) is an acute phase protein, synthesized by hepatocytes. After stimulus, serum concentration of CRP rises quickly, with elevated concentrations found after 6 hours, and a peak production after 48 hours. CRP is a sensitive, though non-specific marker of inflammation, infection and tissue damage (39). Although CRP levels do not allow differentiation between bacterial or viral origin of an infection in adults or children, they are proxy for the disease severity (38,40,41). In adults, point-of-care C-Reactive Protein has added value in the diagnosis of pneumonia, and low values of CRP help to rule out pneumonia (42–44). Measuring point-of-care CRP resulted in a reduction of antibiotic prescription rates for adults with acute respiratory tract infections in primary care (45). Following this evidence, current guidelines recommend using point-of-care CRP to aid in diagnosis and management of pneumonia in adults (10,46). As a result, more than half of all Dutch GPs now have access to point-of-care CRP testing, in daytime practice as well as at out-of-hours services (47,48).

Although point-of-care CRP is also of diagnostic value for diagnosing pneumonia in children (49)

and is useful in ruling out serious infection in children (50), its effect on antibiotic prescription in children with symptoms of LRTI is unclear. There are several reasons to hypothesize that the antibiotic reduction found in trials with adults, cannot be directly translated to the pediatric population. First, children are often viewed as a vulnerable group (27,28). Consequently, children might more often be prescribed antibiotics 'just in case', if a GP is anxious that a serious illness can develop. Furthermore, communication is known to influence prescribing decisions. In a consultation with a sick child, communication will mainly be between a GP and a parent. Parental anxiety and requests for further explanation can be misinterpreted by a GP and perceived as a wish for antibiotic treatment, which might in turn influence prescribing behavior (51).

FEASIBILITY OF MEASURING C-REACTIVE PROTEIN IN CHILDREN

If point-of-care CRP measurement is proven effective, knowledge of GPs' perceptions of CRP measurement in children with acute cough is essential for implementation. The uptake of a new diagnostic instrument is highly dependent on perceptions of users (52). Though sometimes overlooked, this aspect may be as important as an assessment of the effectiveness of the diagnostic intervention itself.

Qualitative studies show that for adult patients, point-of-care CRP enhances patients' and GPs' confidence in prescribing decisions as it supports the diagnostic and therapeutic process and helps GPs to manage patients' expectations for antibiotic treatment for LRTI (53,54). Disadvantages mentioned are difficulties with the interpretation of test results and possible distraction from clinical reasoning when using a diagnostic device (54). Similar to the reasons why the results found in trials with adults may not necessarily apply to children, GPs may also evaluate the use of a diagnostic test differently in children.

AIM OF THIS THESIS

The aim of this thesis was to further investigate a child with suspected RTI in primary care. We aimed to further explore the burden of this common disease and the impact it has on a child's family. Second, we aimed to identify factors that could aid a GP in the diagnosis of children with suspected LRTI. From this, we reach the main aim of this thesis: to study the acceptability and effectiveness of introducing point-of care CRP for the diagnosis of children with a suspected non-serious LRTI.

Our main research questions were:

1. What is the impact of RTI on the general wellbeing of children and their parents?
2. What is the diagnostic value of signs, symptoms and additional diagnostic tests for pneumonia in ambulant children with signs of a respiratory tract infection?

3. Do GPs' perceptions of the use of point-of-care CRP testing in the diagnostic evaluation of children with LRTI differ from their perceptions of the use of this test in adults, and if so in what respect?
4. Does introduction of point-of-care CRP to the diagnostic process of LRTI in children in primary care reduce prescription of antibiotics?

OUTLINE OF THIS THESIS

The first part of this thesis concerns the first two research questions, and focuses more in general on a child with RTI in general practice. In chapter two we describe the burden of disease and the self-management by parents in a cohort of children with RTI. In chapter three we further explore the problem of diagnostic uncertainty. To evaluate how a physician can diagnose a child with pneumonia we systematically identify and summarize available evidence of the diagnostic value of history taking, physical examination and additional diagnostic tests for pneumonia in ambulant children with signs of RTI.
The second part of this thesis focuses on the use of point-of-care CRP in children with LRTI. Chapter four is centered around the question whether GPs' perceptions of the use of point-of-care CRP in the diagnostic evaluation of children with LRTI differ from their perceptions of the use of this test in adults, and if so in what respect? Chapter five than includes the results of a cluster randomized trial that assessed whether point-of-care CRP testing in children with a suspected non-serious LRTI reduces antibiotic prescribing compared to usual care without CRP testing.
Finally, the last chapter of this thesis focuses on the importance of performing clinical trials which evaluate interventions or therapies in children. In conducting our trial, we experienced recruiting difficulties related to the specific legislation for performing clinical trials involving children. Administrative and legal issues can seriously hamper trials with children, while it is not clear whether certain obligatory requirements are necessary in low risk trials with children in primary care. Difficulties we experienced are described, with suggestions for improvement.

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CHAPTER 2

Burden of disease in children with respiratory tract infections in primary care: diary-based cohort study

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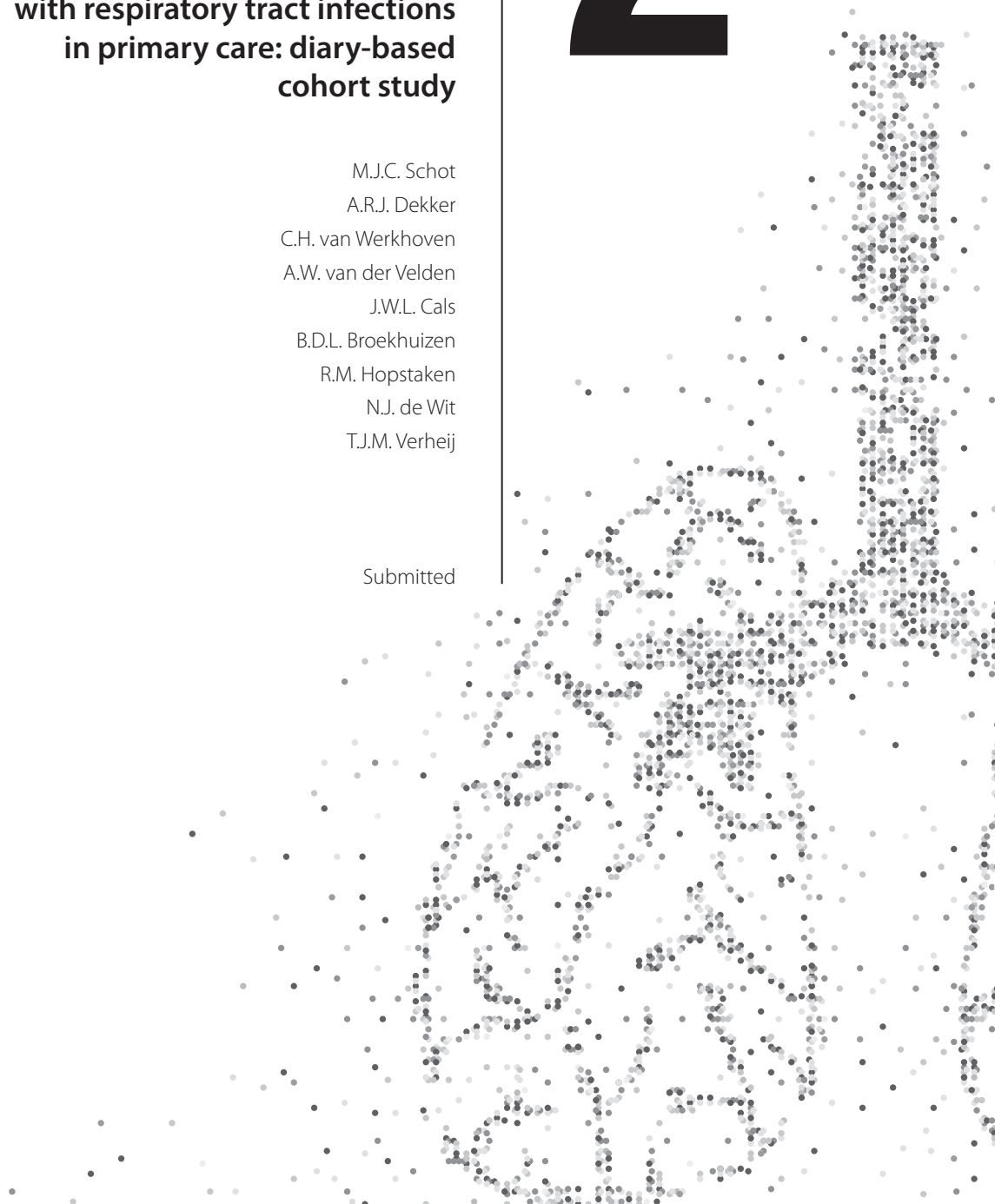


ABSTRACT

Background

Respiratory tract infections (RTI) are a common reason for children to consult in general practice. Antibiotics are often prescribed, in part due to miscommunication between parents and general practitioners (GPs). The duration of specific respiratory symptoms has been widely studied. Less is known about illness related symptoms and the impact of these symptoms on family life, including parental production loss. Better understanding of the natural course of illness related symptoms in RTI in children may improve GP-parent communication during RTI consultations.

Objective

To describe the general impact of RTI on children and parents regarding illness related symptoms, absenteeism from childcare, school and work, use of health care facilities, and the use of OTC medication.

Methods

Prospectively collected diary data from two randomized clinical trials in children with RTI in primary care (n=149). Duration of symptoms was analyzed using survival analysis.

Results

Disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities are very common during RTI episodes, with disturbed sleep lasting longest. 52% Of the children were absent for one or more days from childcare or school, and 28% of mothers and 20% of fathers reported absence from work the first week after GP consultation. Re-consultation occurred in 48% of the children. OTC medication was given frequently, particularly paracetamol and nasal sprays.

Conclusion

Appreciation of, and communication about the general burden of disease on children and their parents, may improve understanding between GPs and parents consulting with their child.

INTRODUCTION

Respiratory tract infections (RTIs) are amongst the most common diagnoses in primary care, particularly in children (1,2). Though most RTI are self-limiting, antibiotics are often prescribed (3,4). Even in a low prescribing country like the Netherlands, 48-63% of antibiotic prescriptions for RTI in children are considered to be noncompliant to guidelines (5,6). Overprescription of antibiotics is driven by diagnostic and prognostic uncertainty, and by poor communication between GPs and parents (7–9). A systematic review reported that GPs often considered acute illness as a purely medical problem. This contrasted with parents voicing concerns of for example missing school. This mismatch led GPs to interpret these concerns as resistance to diagnosis or to treatment decisions, and as an implicit request for antibiotics. This might influence prescribing decisions (7). It has been suggested that a more bio-psycho-social approach may avoid some of the miscommunication (7). Duration of respiratory symptoms in children, such as cough and nasal congestion, has been studied previously (10–12). After one week, symptoms in 75% of children have improved, but half may still be coughing. Cough recovers by 25 days in 90% of the children. Recently, a large cohort study examined patterns in recovery from cough and found 66% of children was recovered by day 7, while 16% of children had persistent symptoms after 15 days (13). GPs tended to underestimate the duration of symptoms (10). However, besides causing symptoms, RTI influences a child's daily functioning in general, for example impacting on sleeping, eating and school attendance. This impacts on family life. For example, disturbed sleep was reported by 72% of parents with children with acute cough (14). Furthermore, missed days at childcare or school may induce work absenteeism for parents, also adding to the burden of this common illness (15,16). A previous study reported reduced quality of life in parents of children with influenza-like-illness, with total time spent caring for a child and severity of illness as factors independently associated to quality of life (17).

Awareness of the type and extent of the broader impact of RTI on families may contribute to a better understanding between GPs and parents, better-informed management decisions and improved counseling of parents. We therefore studied the impact of RTI on children and their parents, with respect to duration of illness related symptoms, absenteeism from childcare, school and work, use of health care facilities, and the use of OTC medication in a cohort of children with RTI.

METHODS

Study design

This observational diary-based study used data from two Dutch randomized clinical trials in children with RTI in primary care (see supplementary data for further details on the trials). Both trials aimed at reducing antibiotic prescriptions for children with RTI, the first through an online training for GPs and an information booklet for parents (18), and the second by introducing point-of-care CRP

measurement in children with RTI (19). In both studies, parents were asked to fill out similar daily diaries. To avoid impact of the trial interventions on the results of this cohort study, we only studied children in the control group of both trials. This ensured that children studied received usual care for RTI in general practice.

Study population

We included children that were aged between three months and 12 years old, diagnosed with an acute RTI. Detailed eligibility criteria for the two RCTs are listed in the Supplementary data. For the purpose of this study, we grouped children based on the diagnosis as registered by the treating GP. ICPC based diagnoses were dichotomized into upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) (Supplementary data).

Data collection

Patient characteristics: sex, age, diagnosis by ICPC-code, and if applicable prescription of antibiotics were noted by the GP on the day of inclusion.

Parents kept a 14-day diary. At baseline these included general questions on child characteristics and previous use of OTC medication. Second, the diary assessed daily symptoms through a list of symptoms to be rated daily on a 5-point-Likert scale ranging from 0 (no symptoms present) to 4 (very major problem). Illness related symptoms rated were disturbed sleep, decreased intake of food and/or fluid, feeling ill and disturbance at play or other daily activities. Respiratory symptoms similarly ranked were cough, phlegm, dyspnea, wheezing and nasal congestion. Finally, diaries contained weekly questions concerning the use of OTC medication, the use of health care facilities and the absence from childcare, school and parents' work related to the child's illness.

Outcomes

We defined three major outcomes:

1. Duration of illness related symptoms: disturbed sleep, decreased intake of food and/or fluid, feeling ill, and disturbance at play or other daily activities.
2. Impact on family life, defined as the number of days children were absent from school or childcare, the number of hours parents were absent from work and the use of the health care system.
3. Use of OTC medication.

Duration of illness related symptoms

The scores for four illness related symptoms were summed to create a daily score of illness related symptoms, with a maximum of 16 points. This score on day 1 was used as a proxy for severity of illness related symptoms on the day of consultation. We regarded a child to be recovered on the first day none of these symptoms was ranked as a 2 (moderate problem) or higher, irrespective of subsequent

values. We applied the same strategy to the respiratory symptoms, with a maximum score of 20 points.

Impact on family life

The number of days a child was absent from childcare or school was evaluated weekly after the consultation. Time off work by parents is presented as hours missed per week. Use of healthcare facilities was analyzed in four predefined categories: contact with GP, contact with out-of-hours service, contact with pharmacy and contact with hospital (either ER or specialist).

Use of OTC medication

Use of OTC medication was scored weekly, in four predefined categories: paracetamol, NSAID, cough medication and nasal sprays.

Analysis

Missing values for the baseline characteristics gender (n=1), duration of symptoms before consultation (n=6) and score for severity of symptoms (n=16) were imputed using multiple imputation (20).

For patients with missing daily symptom scores, if the last entered value was scored as a 2 or higher this was considered as a real missing value, and data was censored from that day on for the survival analysis. When no use of health care facilities, absence from day care, school or parents' work was noted, it was assumed absent. When no medication was listed in the diary, it was assumed no medication was given.

All analyses were performed for the total group of children and separately for the two diagnostic categories: URTI and LRTI. As LRTI is generally regarded as a more severe illness, we hypothesized that outcomes might differ between the groups.

Recovery rates were analyzed using survival analysis using Kaplan-Meier plots. We used a log-rank test to determine whether there were statistical differences in recovery rates between children with URTI and LRTI. Secondary analysis was conducted using multivariable Cox regression to determine which of the baseline characteristics were associated with time to recovery of symptoms, and hazard ratios were calculated. A hazard ratio <1 indicates a longer time to recovery of symptoms. Given the two diagnostic categories, this resulted in four models. Model fit was checked for each of the four models, testing for collinearity between variables by calculating variance inflation factors, proportional hazards, and linearity of continuous predictors. The proportional hazards assumption was not met for the baseline variable of illness related symptoms and respiratory symptoms in children with URTI, and for illness related symptoms in children with LRTI. Therefore, we used time transformation of this variable in the analysis. Finally, we evaluated duration of each of the four illness related symptoms separately.

We tested statistical significance of categorical variables using Chi-square test or Fisher's exact test, as appropriate. All descriptive analyses we performed using SPSS statistics version 24. Multiple imputation, survival analysis and Cox regression analysis were performed using R version 3.5.1.

RESULTS

A total of 149 diaries (41% of total number of children in control groups of both trials) were available for analysis (67 URTI and 82 LRTI). Mean age in both groups was 3 years (SD 2.9 (URTI) 2.6 (LRTI)). Mean duration of illness before consultation was 4.7 and 7.0 days for URTI and LRTI respectively. During the first consultation, children with LRTI were prescribed antibiotics more often compared to children with URTI (52% vs. 42%). The summed score of illness related symptoms was higher in children with LRTI. Baseline characteristics are listed in Table 1.

Table 1. Baseline characteristics of 491 children consulting the GP with respiratory tract infection

	URTI (n=67)	LRTI (n=82)
Male sex, n (%)	31 (47%)	37 (45%)
Mean age, years (SD)	2.8 (2.9)	2.9 (2.6)
Siblings, n (%) yes	39 (58%)	59 (72%)
Child care or school attendance, n (%)	56 (83.6%)	68 (82.9%)
Mean pre-consultation illness duration, days (SD)	4.7 (3.1)	7.0 (5.5)
Mean general symptom severity score (SD)	8.3 (4.3)	9.1 (4.1)
Mean respiratory symptom severity score (SD)	6.9 (4.6)	10.7 (4.1)
Antibiotics prescribed, n (%)	28 (42%)	43 (52%)

Duration of illness related symptoms

On the day of consultation, 90% of parents of children diagnosed with URTI and 94.2% of children diagnosed with LRTI reported disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities as more than a moderate problem (score ≥ 2). On day 7, this was 13.8% in the URTI group versus 27.8% in LRTI group, and this declined to respectively 4.5% and 13.9% on day 14. Overall, the median time from the first consultation to reported recovery of illness related symptoms in children with URTI was 4 days versus 5 days in children with LRTI (p=0.004, figure 1a).

Duration of the separate illness related symptoms are shown in table 2. Sleep disturbance persisted most, with a mean duration of 3.1 and 4.3 days for URTI and LRTI, respectively.

A higher baseline score for illness related symptoms was associated with longer duration of symptoms in children with URTI (Hazard Ratio 0.63 on day 1, 95% CI 0.51-0.79). For children with LRTI three factors were associated with duration of symptoms: baseline score for illness related symptoms (HR 0.50 on day 1, 95% CI 0.36-0.69), age (HR 1.17, 95% CI 1.04-1.32) and prescription of antibiotics (HR 2.46, 95% CI 1.46-4.13) (see Supplementary data for all hazard ratios).

Respiratory symptoms were reported by parents to be moderate to severe for 87.1% of children with URTI and for 100% of children with LRTI on the day of consultation. Respiratory symptoms decreased during follow-up, with parents reporting symptoms still more than a moderate problem

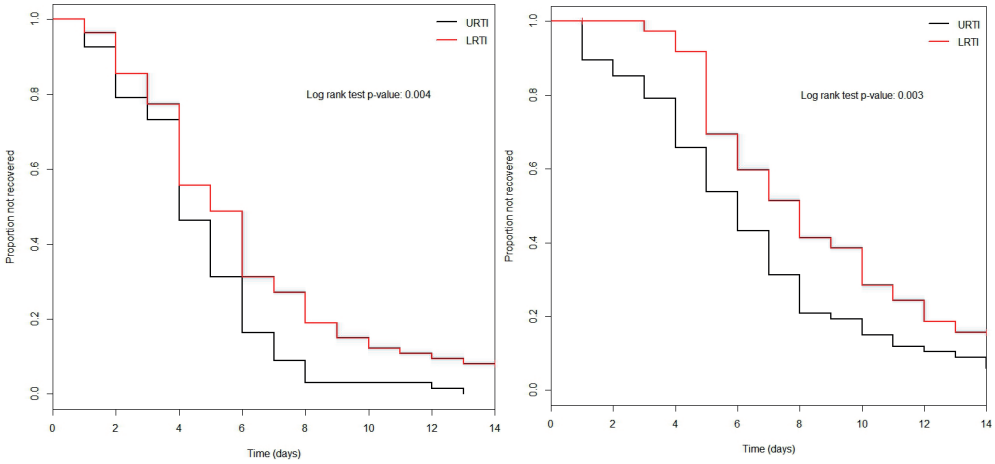
on day 14 in 7.5% of children with URTI and in 25.4% of children with LRTI. Overall, the median time to reported recovery of respiratory symptoms in children with URTI was 6 days versus 8 days in children with LRTI (p=0.003, figure 1b).

Table 2. Mean duration of illness related symptoms (days and 95% confidence interval), result of Kaplan-Meier analysis.

	URTI	LRTI
Disturbed sleep	3.1 (2.6-3.7)	4.3 (3.5-5.1)
Decreased intake of food and/or fluid	2.9 (2.2-3.5)	3.2 (2.6-3.8)
Feeling ill	2.3 (1.8-2.9)	3.7 (3.1-4.4)
Disturbance at play or other daily activities	2.4 (1.9-3.0)	3.3 (2.6-4.0)

URTI: upper respiratory tract infection
LRTI: lower respiratory tract infection

Figure 1. Recovery from illness related symptoms and respiratory symptoms in days for children with URTI and LRTI
Panel 1: Recovery from illness related symptoms
Panel 2: Recovery from respiratory symptoms



URTI: upper respiratory tract infection
LRTI: lower respiratory tract infection

Impact on family life

More than half of the children were absent from childcare or school during the first week after consultation, for a median of 2 days. 28% Of mothers and 20% of fathers took time off work for a median of 8 hours during the first week. Nearly a quarter of parents reported to have made extra

arrangements for childcare during that week (LRTI 15% versus URTI 32%, difference 17%, p-value 0.02) (table 3). Absenteeism decreased during the second week after consultation with 13% of children being absent at childcare or school, and 5% of mothers and 4% of fathers being absent at work. In the second week, significantly more fathers took time of work if their child was diagnosed with LRTI, compared to URTI (7% vs 0%, p=0.03)

In the week after the first consultation 48% of children reconsulted the GP, and 7% of children visited an out-of-hours service. The pharmacy was visited by 36% of parents in the first week, compared to 4% in the second week (table 3).

Table 3. Diary reported absenteeism and use of the health care system after visiting a general practioner

	Week 1				Week 2			
	URTI (n=67)	LRTI (n=82)	Total (n=149)		URTI (n=67)	LRTI (n=82)	Total (n=149)	
	n (%)	n (%)	n (%)	Median (range)	n (%)	n (%)	n (%)	Median (range)
Absent from childcare or school	32 (48%)	45 (55%)	77 (52%)	2 days (1-5)	5 (7%)	14 (17%)	19 (13%)	1 day (1-5)
Mother absent from work	13 (19%)	28 (34%)	41 (28%)	8 hours (1-16)	1 (2%)	6 (7%)	7 (5%)	8 hours (1-8)
Father absent from work	9 (13%)	21 (26%)	30 (20%)	8 hours (1-25)	0*	6 (7%)*	6 (4%)	8 hours (1-24)
Need for extra childcare	10 (15%)*	26 (32%)*	36 (24%)		0	3 (4%)	3 (2%)	
Contact with GP office, phone	3 (4,5%)*	16 (20%)*	19 (13%)		0	2 (2%)	2 (1%)	
Contact with GP in practice	26 (39%)	45 (57%)	71 (48%)		1 (2%)	5 (6%)	6 (4%)	
Contact with OOH service	3 (5%)	7 (14%)	10 (7%)		0	2 (2%)	2 (1%)	
Contact with hospital	1 (2%)	3 (4%)	4 (3%)		0	5 (6%)	0	
Contact with pharmacy	22 (33%)	31 (39%)	53 (36%)		1 (2%)	0 (0%)	6 (4%)	

*Statistically significant difference between children with URTI and LRTI with p-value <0,05.
URTI: upper respiratory tract infection
LRTI: lower respiratory tract infection

Use of OTC medication

OTC medication was given to the majority of children and was highest in the week before the consultation (86.6%). Paracetamol was given most frequently throughout the entire follow-up period, followed by nasal spray and cough syrup (table 4).

Table 4. Diary-reported use of over the counter medication

	Week before consultation			Week 1			Week 2		
	URTI (n=67)	LRTI (n=82)	Total (n=149)	URTI (n=67)	LRTI (n=82)	Total (n=149)	URTI (n=67)	LRTI (n=82)	Total (n=149)
Use of OTC (total)	60 (90%)	69 (84%)	129 (86.6%)	48 (72%)	53 (65%)	101 (67.8%)	9 (13%)	17 (21%)	26 (17.4%)
Use of paracetamol	50 (75%)	56 (68%)	106 (71.1%)	37 (55%)	38 (46%)	75 (50.3%)	5 (8%)	10 (12%)	15 (10.1%)
Use of NSAID	1 (2%)	1 (1%)	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Use of cough syrup	22 (30%)	28 (34%)	48 (32.2%)	11 (16%)	20 (24%)	31 (20.8%)	2 (3%)	5 (6%)	7 (4.7%)
Use of nasal spray	27 (40%)	27 (45%)	54 (43%)	20 (30%)	32 (39%)	52 (34.9%)	5 (8%)	9 (11%)	14 (4.9%)

OTC: over the counter medication
NSAID: non-steroid anti-inflammatory drug
URTI: upper respiratory tract infection
LRTI: lower respiratory tract infection

DISCUSSION

Summary of main findings

RTI in children have a profound effect on the general wellbeing of children consulting in general practice. On the day of consultation more than 90% of children experiences disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities. Disturbed sleep persisted longest. Overall, respiratory symptoms persist longer than illness related symptoms. The severity of symptoms on the day of consultation was related to the duration of symptoms throughout the follow-up period. Approximately half of the children were absent for one or more days from childcare or school, and 28% of mothers and 20% of fathers reported absence from work for eight hours on average. Re-consultation occurred in almost half of the children. OTC medication was given frequently to children with RTI, particularly paracetamol and nasal sprays.

As LRTI is generally regarded as a more serious illness, we decided to analyze duration of symptoms separately for the two groups. Although we found statistical differences in duration of symptoms, the absolute differences were minimal. Children with URTI and LRTI did not differ significantly in absence from childcare or school and reconsultation with a GP.

Strengths and limitations

Unique to our study is the more detailed description of illness related symptoms associated with the wellbeing of a child with RTI. Diary data in both studies were collected longitudinally in daily diaries. The daily collection of symptom scores minimized the probability of recall bias. The use of data collected in two different trials provided a larger group of children with URTI and LRTI.

A possible limitation of our study was the representativeness of the sample. 41% Of all parents in both trials returned the diaries. However, children with and without returned diaries did not differ significantly at baseline in the trials (data not shown). Whether duration of symptoms or severity of symptoms influenced the return rate of the diaries is unknown. It is possible that this affects the generalizability of the results. Furthermore, our results regard families consulting for RTI, and may not necessarily apply to (the majority of) children who do not visit a GP (16). The reported diary-recorded duration of symptoms is the duration of symptoms after the first GP consultation. This was a mean of 4.7 and 7 days after the URTI and LRTI onset, respectively. The presented data therefore probably underestimate the impact of a complete disease episode. However, our aim was to inform GPs about the impact of an RTI on a child and its parents at the moment of consultation, therefore this selected group does provide useful information. Finally, although we found certain factors that were significantly related to recovery of symptoms in this cohort, our study was not designed to determine causal effects. The identified determinants need further exploration to determine whether they are causally related to illness duration.

Comparison with existing literature

Recovery rates for respiratory symptoms in our cohort were similar to rates found in other studies (10,11,21,22). A recent study found absenteeism in 28% of parents when their child had an infectious episode, with a median of 2 days. This is lower than the nearly fifty percent we found, possibly because these children were probably less ill, as only a minority of these children visited a GP (16). Previous studies have shown that this affects quality of life in parents, and is also a main driver of total societal costs of RTI (15,17,23,24).

A previous study in adults reported comparable rates of self-medication in patients with RTI (25), most often paracetamol. Paracetamol is useful for treating pain and fever but evidence on its effect on wellbeing is lacking, although it is likely that treating fever and pain would lead to improvement of wellbeing (26,27). There is no evidence for effectiveness of other OTC medication for the treatment of RTI symptoms in children (28,29). These medications are however still recommended by physicians (30,31). A qualitative study found that GPs usually did not recommend OTC medication for cough and cold, but parental anxiety and the need to "do something" sometimes influenced their recommendations (31).

Reconsultation rates differ in various studies (11,21,32), but are generally lower than the 48% we found. We hypothesize that this may be due to an accessible primary health care system in the Netherlands.

Implications for practice and further research

As the reason for encounter in consultations for RTI is not only determined by respiratory symptoms but also by their consequences, it is important that a GP is aware of the impact RTI has on a child and its family. Fear of complications and duration of symptoms may increase consultation rates (11). Being able to adequately communicate and reassure parents about the general symptoms of RTI, and appreciation of the impact of disturbed sleep or diminished appetite will increase the mutual understanding between parents and GP. Furthermore, this knowledge about the illness related impact might help the GP to make the most appropriate management decisions. Finally, better appreciation of the impact of the child's illness on the parents and a shared decision-making process will improve the parents' compliance with the RTI management of the GP. Disease impact should be incorporated alongside information on respiratory symptoms in patient information in leaflets and websites.

Knowledge about the frequency of OTC medication use and its drivers, may further facilitate shared decision making between parents and GPs. GPs have a task in informing parents, and the use of OTC medication must be balanced against costs and possible side-effects. Robust evidence of effectiveness is not available for most of the medications used (27–29). However, wellbeing may be improved by the use of paracetamol or NSAIDs.

We noticed that children often reconsulted their GP. Further research might focus on reasons for this healthcare seeking behavior, and may help identify strategies to reduce unnecessary reconsultations and enhance self-management.

CONCLUSION

RTI impacts not only on a child's general wellbeing but also on family life as nearly half of the children stay home from childcare or school during the first week after consultation, and nearly half of the parents are absent from work. OTC medication is given to the majority of the children during the first week after consulting their GP. Communication about this general impact of RTI can improve understanding between GPs and parents and enhance shared decision-making.

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Supplementary data 1: Additional information and inclusion criteria of the randomized controlled trials which supplied data

The PRICE-study ("Point-of-care C-reactive protein to assist in primary care management of children with lower RTI") is a cluster randomized controlled two arm trial to investigate the effects of POC CRP measurement in children. 28 Primary care practices and four out-of-hours services in the Netherlands were randomly allocated to either usual care for children with non-severe lower RTI or usual care in combination with point-of-care C-reactive protein measurement for these children.

Eligibility criteria for the PRICE study:

Inclusion (all criteria must be present)	Exclusion (any presence of)
Suspicion of LRTI	Impaired immunity
Age 3 months – 12 years	Severe pulmonary disease
Acute cough < 21 days	Serious congenital defects
Reported fever >38 °C, < 5 days	Use of systemic antibiotics and/or corticosteroids in past 4 weeks
	Judged severely ill by the GP based on symptoms and signs
	Highly suspected of having pneumonia by the GP
	Referral to specialist or emergency department deemed necessary by GP

RAAK ("Rational Antibiotic use Kids with RTIs") is a cluster randomized controlled trial among 32 primary care practices. Usual care was compared to a two-faceted intervention: an online training for GPs concerning relevant guidelines, including the problem of over-prescription and education on communication skills. This was combined with an information leaflet for parents about RTIs and antibiotics.

Eligibility criteria for the RAAK study: Age < 18 years presenting with symptoms of any RTI, including ear infection

Supplementary data 2. Diagnostic categories based on ICPC codes

Category	ICPC-code
Lower RTI	Wheezing (R03) Cough (R05) Whooping cough (R71) Acute laryngitis/tracheitis (R77) Acute bronchitis/bronchiolitis (R78) Pneumonia (R81) Asthma or bronchial hyperreactivity (R96)
Upper RTI	Acute upper RTI (R74) Acute (rhino)sinusitis (R75) Acute tonsillitis or peritonsillar abscess (R76) Sore throat (R21) Hypertrophic or chronic infection tonsils (R90) Acute lymphadenitis (B70) Ear pain (H01) Ear discharge (H04) Acute otitis media (H71) Otitis media with effusion (H72) Other ear infections (H74) Perforated eardrum (H77)

Supplementary data 3. Predictors of duration of illness related symptoms until less than a moderate problem, results from Cox regression

	URTI				LRTI			
	HR	95% CI		P-value	HR	95% CI		P-value
Antibiotics	1.41	0.81	2.45	0.23	2.46	1.46	4.13	<0.01
Sex (girl)	1.34	0.78	2.31	0.28	0.78	0.45	1.34	0.37
Siblings	1.09	0.59	2.00	0.79	0.52	0.26	1.04	0.06
Age	0.95	0.86	1.04	0.28	1.17	1.04	1.32	0.01
Child care or school attendance	1.63	0.80	3.33	0.18	0.67	0.31	1.44	0.30
Pre-consultation illness duration	0.96	0.88	1.05	0.39	0.96	0.92	1.01	0.11
General symptom severity score	0.63*	0.51	0.79	<0.01	0.50*	0.36	0.69	<0.01

*Adjustment using time transformation, reported hazard ratio is hazard ratio on day 1; on subsequent days, log(hazard ratio) is divided by day number.

CHAPTER 3

Diagnostic value of signs, symptoms and diagnostic tests for diagnosing pneumonia in ambulant children in developed countries: a systematic review

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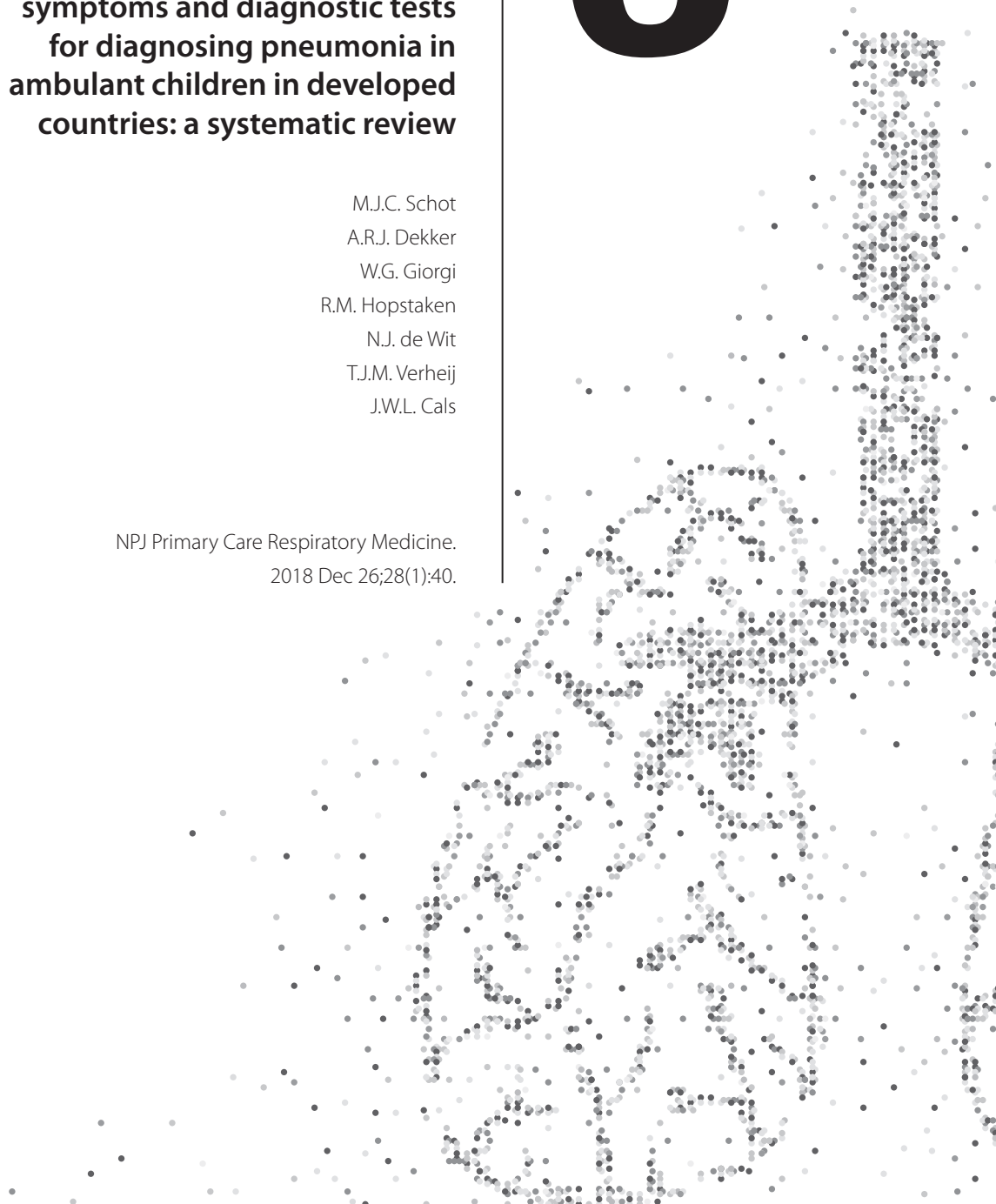

ABSTRACT

Identifying a child with pneumonia in the large group of children with acute respiratory tract infections can be challenging for primary care physicians. Knowledge on the diagnostic value of specific signs and symptoms may guide future decision rules and guidelines for clinicians. We aimed to identify and systematically review available evidence for the diagnostic value of signs, symptoms and additional tests to diagnose pneumonia in children in an ambulatory setting in developed countries. We conducted a systematic review, searching in the electronic databases of PubMed and Embase. Quality assessment of studies was done using the QUADAS-2 criteria. After data extraction from selected studies, we calculated and summarized test characteristics (sensitivity, specificity, negative and positive predictive values) of all available signs, symptoms, additional laboratory tests and chest ultrasonography. The original search yielded 4665 records, of which 17 articles were eligible for analysis; 12 studies on signs and symptoms, four on additional laboratory tests and six on ultrasonography. All included studies were performed in a secondary care setting. Risk of bias was present in the majority of studies in the domain of patient selection. Prevalence of pneumonia varied from 3.4%-71.7%. The diagnostic value of the available 27 individual signs and symptoms to identify pneumonia was low. In a low prevalence setting (4 studies, pneumonia prevalence <10%) clinically ill appearance of the child and oxygen saturation <94% can aid a physician. In a high prevalence setting (10 studies, pneumonia >10%) additional diagnostic tests such as oxygen saturation, C-Reactive Protein and White Blood Count are more promising. Chest ultrasonography showed high diagnostic value in settings with higher prevalence of pneumonia. Single signs and symptoms from medical history and physical examination or individual additional diagnostic tests are insufficient to diagnose pneumonia in ambulant children. Very few diagnostic studies are conducted in settings with low prevalence of pneumonia. Future research in low prevalence settings should focus on the diagnostic value of the combination of clinical features and additional testing possibly using meta-analysis of individual data.

INTRODUCTION

Acute respiratory tract infections in children are very common, and one of the most important reasons to consult the general practitioner (GP), pediatrician or emergency physician in developed countries (1–3). Most children will suffer from a non-serious, self-limiting infection, but it is important to adequately identify a child with pneumonia. Even in high income countries including the UK and USA, lower respiratory tract infection is estimated to cause around 34 deaths per 100 000 children per year and cost 173 000 disability-adjusted life-years per year in children younger than 5 years (4). However, correctly identifying an ambulant child with pneumonia, warranting prescription of antibiotics is difficult (5–9). Consequently, over-prescription of antibiotics is common (10–12). Antibiotics may cause side effects (13), increase re-consultation rates (14) and repeated use of antibiotics increases antimicrobial resistance in communities and individuals (15,16).

Diagnostic uncertainty plays an important role in over-prescription of antibiotics in children (10–12,17,18). Physicians in ambulatory settings still mainly rely on history taking and clinical examination for diagnosis and management decisions. With developing technology, access to additional diagnostic tests in ambulatory settings is increasing, with tests also becoming available as point-of-care tests. For example, point-of-care C-reactive protein (CRP) measurement is increasingly available, and recommended by guidelines to aid in diagnosis and management of pneumonia in adults (19–22). Although there is currently no accurate biomarker available to distinguish between a bacterial or viral infection (23), biomarkers may support correct identification of children at risk of serious infections in ambulatory care (24). This might help primary care physicians decide which children with suspected pneumonia need to be more closely monitored, or which might benefit from antibiotic treatment.

Systematic reviews have reported separately on the diagnostic value of clinical features (5,25) and laboratory tests (26) to identify children with serious infections including pneumonia. These reviews identified shortness of breath, increased work of breathing and hypoxemia as most important to identify the presence of pneumonia. However, a lack of evidence particularly to identify children with serious infections in primary care was identified. Currently available decision rules for pneumonia showed value in ruling out the need for hospitalization in a child with suspected pneumonia. The rate of false positives when applying this decision rule is high (27,28). These decision rules do not aid the physician in identifying the ambulatory child in need of antibiotics. To our knowledge a systematic review integrating information on all signs, symptoms, and additional tests currently available in ambulatory settings to diagnose pneumonia has not been performed.

The aim of this study was to therefore systematically identify and summarize available evidence of the diagnostic value of signs, symptoms and additional diagnostic tests for confirming pneumonia or safely ruling it out in ambulant children with signs of a respiratory tract infection in developed countries.

RESULTS

Study selection and characteristics

The initial search identified 4306 articles (November 2016) with a further 359 at the November 2017 update. Three studies were identified through reviewing reference lists (figure 1). After reviewing titles and abstracts, 133 articles were selected for full-text evaluation. Seventeen studies met all the inclusion criteria and were selected for the final data extraction. All selected studies were performed in a secondary care ambulatory setting. 12 Studies reported on signs and symptoms, 4 on laboratory tests and 6 on the use of ultrasonography. Table 1-3 show the characteristics of the selected studies, with the study of Oostenbrink et al. reporting diagnostic values of index tests in three different patient populations. The prevalence of pneumonia in the selected studies varied from 3.4% to 71.7%. Table 4 shows the outcomes of the quality assessment of the included studies. Risk of bias was present in the majority of the studies in the domain of patient selection. These studies included only children with an indication for CXR.

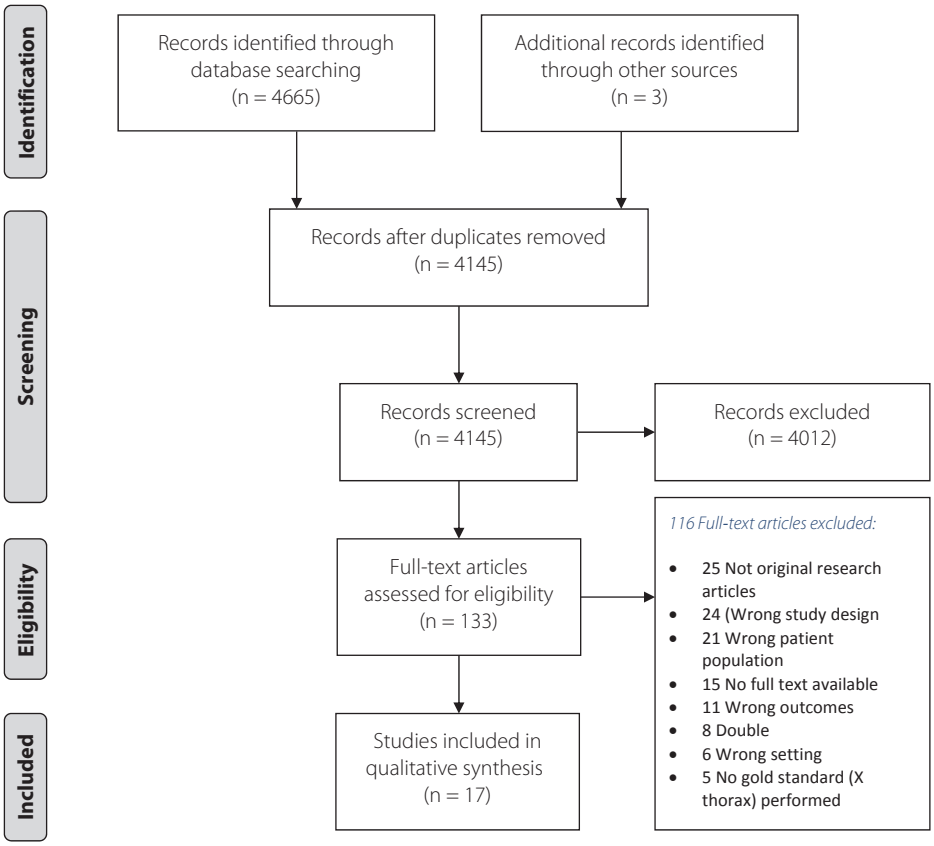

Table 1. Characteristics of selected articles reporting on signs and/or symptoms

Nr.	Author	Setting	% with pneumonia	Age range	Inclusion criteria	Exclusion criteria	Index test	Reference standard
1	Ayalon (2013) (8)	ED, Israel	34%	1 month – 16 years	CXR for suspicion of pneumonia	Hospital acquired pneumonia, aspiration pneumonia	Signs and symptoms	CXR
2	Craig (2010) (37)	ED, Australia	3.4%	≤5 years	Fever measured or reported by parents within previous 24 hours	Transferred from another hospital, cancer, transplant recipients	Signs and symptoms	CXR
3	Lynch (2004) (6)	ED, Canada	35,7%	1 – 16 years	CXR for suspicion of pneumonia	Chronic respiratory disease, chronic congenital or complex cardiac disease, gastroesophageal reflux, sickle cell disease, malignancy, spastic quadriplegia, asthma requiring >1 bronchodilator treatment at ED, pneumonia in past 8 weeks, critically ill patients	Signs and symptoms, vital signs	CXR
4	Mahabee (2005) (38)	ED, USA	8.6%	2 – 59 months	Cough and one of the following: labored, rapid, or noisy breathing; chest or abdominal pain; fever	Currently taking antibiotics; treatment for smoke inhalation, foreign body aspiration, or chest trauma; known diagnoses of asthma, bronchiolitis, cystic fibrosis, sickle cell disease, or chronic cardiopulmonary disease	Signs, symptoms and vital signs	CXR
5	Nijman (2013) (39)	ED, the Netherlands	6,7%	1 month – 15 years	Fever noted in 24 hours before presentation or ≥38.0°C at ED	Chronic comorbidity, received antibiotics in past week	Signs and symptoms	CXR, one-week follow-up
6.1	Oostenbrink (2013) (35)	ED, the Netherlands	16%	1 month- 16 years	Rectal temperature ≥38.0°C and cough	Immunodeficiency, multiple handicaps, pre-existing pulmonary disease	Signs, symptoms, vital signs, WBC, CRP	Composite: CXR, or follow-up, or review of records
6.2	Oostenbrink (2013)	ED, UK	14%	1 month- 16 years	Axillary temp ≥38.0°C and lower respiratory signs	Immunodeficiency	Signs, symptoms, vital signs, WBC, CRP	Composite: CXR, or follow-up, or review of records

Table 1. continued

Nr.	Author	Setting	% with pneumonia	Age range	Inclusion criteria	Exclusion criteria	Index test	Reference standard
6.3	Oostenbrink (2013)	ED, UK	3.7%	1 month- 16 years	Fever reported or measured rectally ≥38.5°C and acute breathing difficulty	Immunodeficiency, multiple handicaps, admitted for resuscitation	Signs, symptoms, vital signs, WBC, CRP	Composite: CXR, or follow-up, or review of records
7	Rothrock (2001) (29)	ED, USA	20%	≤5 years	Presenting to ED, requiring CXR	CXR obtained for trauma, foreign body ingestion, submersion injury	Canadian task force guideline	CXR
8	Shah (2010) (30)	ED; USA	14.5%	≤5 years	CXR for suspicion of pneumonia	CXR for other indications than pneumonia, known illness that placed patient at greater risk of pneumonia	Tachypnoea	CXR
9	Shah (2013) (34)	ED, US	18%	0 – 21 years	Clinically suspect of pneumonia, requiring CXR	Hemodynamic instability	Ultrasound	CXR
10	Urbankowska (2015) (31)	Dept. ped. pulmonology & allergy, Poland	72%	> 1 month	Fever > 38.0°C, dyspnea, cough, and abnormal long auscultation	Hospital acquired pneumonia, persistent abnormalities on former CXR, treated for pneumonia in last 4 weeks	Signs, symptoms, CRP, WBC	CXR
11	Wingerter (2012) (32)	ED; USA	16%	≤5 years	CXR for suspicion of pneumonia	Known illness that placed patient at greater risk of pneumonia	WHO criteria for diagnosis of pneumonia	CXR
12	Zukin (1986) (33)	ED, USA	14%	< 17 years	Clinically assessed need for CXR	None	Signs and symptoms	CXR

Abbreviations:
ED: emergency department, CXR: chest X-ray, WBC: white blood cell count, CRP: C-reactive protein

Table 2. Characteristics of selected articles reporting on laboratory tests

Nr.	Author	Setting	% with pneumonia	Age range	Inclusion criteria	Exclusion criteria	Index test	Reference standard
5	Nijman (2013) (39)	ED, the Netherlands	6,7%	1 month – 15 years	Fever noted in 24 hours before presentation or ≥38.0°C at ED	Chronic comorbidity, received antibiotics in past week	Signs and symptoms	CXR, one-week follow-up
6.1	Oostenbrink (2013) (35)	ED, the Netherlands	16%	1 month-16 years	rectal temp ≥38.0°C and cough	immunodeficiency, multiple handicaps, pre-existing pulmonary disease	Signs, symptoms, vital signs, WBC, CRP	Composite: CXR, or follow-up, or review of records
6.2	Oostenbrink (2013)	ED, UK	14%	1 month-16 years	axillary temp ≥38.0°C and lower resp signs	immunodeficiency	Signs, symptoms, vital signs, WBC, CRP	Composite: CXR, or follow-up, or review of records
6.3	Oostenbrink (2013)	ED, UK	3.7%	1 month-16 years	fever reported or measured rectally ≥38.5°C and acute breathing difficulty	immunodeficiency, multiple handicaps, admitted for resuscitation	Signs, symptoms, vital signs, WBC, CRP	Composite: CXR, or follow-up, or review of records
10	Urbankowska (2015) (31)	Department of pediatric pulmonology and allergy, Poland	72%	> 1 month	Fever > 38.0°C, dyspnea, cough, and abnormal long auscultation	Hospital acquired pneumonia, persistent abnormalities on former CXR, treated for pneumonia in last 4 weeks	CRP, WBC	CXR
13	Irwin (2017) (40)	ED, UK	9.8%	<16 years	Fever, requiring blood tests	Immunodeficiency	CRP, WBC, PCT, resistin, NGAL	CXR

Abbreviations:
ED: emergency department, CXR: chest X-ray, WBC: white blood cell count, CRP: C-reactive protein, PCT: procalcitonin, neutrophil gelatinase-associated lipocalin

Table 3. Characteristics of selected articles reporting on ultrasonography

Nr.	Author	Setting	% with pneumonia	Age range	Inclusion criteria	Exclusion criteria	Index test	Reference standard
9	Shah (2013) (41)	ED, US	18%	0 – 21 years	Clinically suspect of pneumonia, requiring CXR	Hemodynamic instability	Ultrasound	CXR
10	Urbankowska (2015) (31)	Dept. ped. pulmonology & allergy, Poland	72%	> 1 month	Fever > 38.0°C, dyspnea, cough, and abnormal long auscultation	Hospital acquired pneumonia, persistent abnormalities on former CXR, treated for pneumonia in last 4 weeks	Ultrasound	CXR
14	Copetti (2008) (42)	ED, Italy	67%	6 months – 16 years	Clinical signs suggesting pneumonia		Ultrasound	CXR
15	Ianniello (2016) (43)	ED, Italy	56%	3 – 16 years	Suspect of pneumonia with fever >38.0°C >3 days and cough		Ultrasound	CXR
16	Samson (2018) (44)	ED, Spain	42.5%	0 – 15 years	Suspicion of CAP, performance of CXR	Known pneumonia on arrival to ED, clinical bronchiolitis, previous antibiotic treatment for this episode, chronic chest diseases	Ultrasound	CXR
17	Zhan (2016) (41)	Ped department, Denmark	50%	0 – 15 years	Suspicion of pneumonia with cough, fever ≥38.5°C, elevated respiratory rate, grunting, nasal flaring, or chest recessions or pulse oximetry <95%	Ultrasound not completed within 24h after inclusion	Ultrasound	CXR

Abbreviations:
ED: emergency department, CXR: chest X-ray, CAP: community acquired pneumonia

Table 4. Quality assessment according to QUADAS-2

Nr.	Author	Patient selection	Index test	Reference standard	Flow and timing
1	Ayalon (2013)	☹	☺	☺	☺
2	Craig (2010)	☹	☺	☹	☺
3	Lynch (2004)	☹	☺	☺	☺
4	Mahabee (2005)	☺	☺	☺	☺
5	Nijman (2013)	☺	☺	☹	☺
6	Oostenbrink (2013)	☺	☺	☹	☺
7	Rothrock (2001)	☹	☺	☺	☺
8	Shah (2010)	☹	☺	☺	☺
9	Shah (2013)	☹	☺	☺	☺
10	Urbanowska (2015)	☺	☺	☺	☺
11	Wingerter (2012)	☹	☺	☺	☺
12	Zukin (1986)	☹	☺	☺	☺
13	Irwin (2017)	☹	☺	☺	?
14	Copetti (2008)	☹	☺	☹	?
15	Ianniello (2016)	☹	☺	☺	?
16	Samson (2018)	☹	☺	☺	☺
17	Zhan (2016)	☹	☺	☺	☺

☺ low risk of bias ☹ high risk of bias ? unclear risk of bias

Diagnostic value of signs and symptoms

In total, the included studies reported on 27 signs and symptoms. Separate diagnostic values of all different signs and symptoms are presented in appendix 2 and 3, for studies with high and low prevalence of pneumonia respectively. Signs and symptoms that were evaluated in two or more studies are discussed below.

High prevalence studies

Ten studies reported on the diagnostic value of signs and symptoms in a setting with a pneumonia prevalence >10% (6,8,29–35). Nine of these studies reported on tachypnoea, but different cut-off points were used. Five studies used the WHO definition of tachypnoea (36). Four of these studies showed specificity ranging from 73-76%, with negative predictive value ranging from 85-91% (Table 5). Cough was the symptom with the highest reported sensitivity (range 71-88%) (Table 6). Diagnostic value of abnormal auscultation was investigated in several studies. Decreased breath sounds was evaluated in four studies, chest retractions, wheezing and the presence of crackles in three studies, and the presence of bronchial breathing, rales and rhonchi in two studies (Table 6). Wheezing, chest retractions and bronchial breathing showed the highest specificity within this group of symptoms (range 71-96%). Classic signs associated with pneumonia such as crackles or decreased breath sounds showed lower diagnostic performance. An oxygen saturation < 94% was assessed in two different studies,

with reported specificity ranging between 92-96%. Of the more general symptoms, ill appearance was analyzed in two studies and showed the highest negative predictive values (range 86-92, Table 7).

Table 5. Diagnostic value of tachypnea in a setting with high prevalence of pneumonia

Nr.	Author	Pneumonia prevalence	Sensitivity	Specificity	PPV	NPV
6.1	Oostenbrink [1]	14%	59.0	72.8	28.4	90.6
8	Shah [1]	14.5%	39.7	73.9	20.4	87.9
9	Shah [1]	18%	41	76	27.3	85.4
7	Rothrock [1]	20%	10	5	3	19
11	Wingerter [1]	16.1%	28.9	75.9	15.9	87.5
1	Ayalon [3]	34%	22.7	89.8	54.0	68.8
3	Lynch [3]	35.7%	13	95	60	66
6.2	Oostenbrink [2]	14%	69.0	67.7	25.5	93.2
12	Zukin [3]	14.4%	50	68	21	89

Cut-of values for tachypnoea: [1]WHO definition [2]APLS criteria [3]other
Abbreviations:
PPV: positive predictive value, NPV: negative predictive value

Table 6. Diagnostic value of assessing breathing and auscultation in a setting with high prevalence of pneumonia

Index test	Study nr.	Pneumonia prevalence	Sensitivity	Specificity	PPV	NPV
Cough	1	34%	78.5	30.2	37.2	72.7
	3	35.7%	88	16	36.8	70.6
Decreased breath sounds	9	18%	24	83	23.7	83.3
	7	20%	9	6	2	20
	3	35.7%	54	55	40,0	68,3
	10	72%	46,1	76,7	83,4	36,0
Wheezing	12	14.4%	6	71	3	82
	3	35.7%	56,0	93	81,7	79,2
	10	72%	3,9	90	49,7	27,00
Crackles	9	18%	24	75	17,4	81,8
	3	35.7%	43	73	47.0	69.7
	10	72%	36.8	60	70.0	27.3

Table 6. continued

Index test	Study nr.	Pneumonia prevalence	Sensitivity	Specificity	PPV	NPV
Chest retractions	6.2	14%	56.9	83.4	35.5	92.4
	6.1	16%	28.2	81.5	21.8	86.1
	3	35.7%	5	98	58.2	65.0
Rhonchi	12	14.4%	78	73	15	86
	10	72%	2.6	80	24.8	24.5
Rales	12	14.4%	57	75	27	90
	7	20%	23	15	7	48
Bronchial breathing	3	35.7%	7	96	49.3	65
	10	72%	17.1	93.3	86.6	30.8
Oxygen saturation <94%	6.2	14%	32.8	92.3	40.4	89.5
	6.1	16%	14.1	96.0	39.3	85.9

Abbreviations:
PPV: positive predictive value, NPV: negative predictive value

Table 7. Diagnostic value of general symptoms in a setting with high prevalence of pneumonia

Index test	Study nr.	Pneumonia prevalence	Sensitivity	Specificity	PPV	NPV
Ill appearance	6.2	14%	79.3	38.7	17.2	92.1
	6.1	16%	33.3	77.9	21.7	86.4
Fever	12	14.4%	94	36	20	97
	3	35.7%	47	68	45	70
Tachycardia	1	34%	35.6	77.3	45.1	69.6
	3	35.7%	51	60	68	41

Abbreviations:
PPV: positive predictive value, NPV: negative predictive value

Low prevalence studies

Four studies reported on the diagnostic value of signs and symptoms in settings with a prevalence of pneumonia < 10% (35,37–39). Diagnostic values of all signs reported on in two or more studies are shown in Table 8. Although NPVs were above 90% for all evaluated signs and symptoms, the additional diagnostic value of signs and symptoms was low given the low pre-test probability. The absence of tachypnoea, crackles and ill appearance showed the most value when ruling out pneumonia, but only decreased the predicted value by 4.8% at most. In some studies, saturation <94%, retractions and ill appearance gave an increase in PPV of up to 27%, but outcomes of different studies varied. As in the

high prevalence settings, the classic symptoms associated with pneumonia such as crackles had low diagnostic value.

Table 8. Diagnostic value of signs in a low prevalence population with CXR confirmed pneumonia

Index test	Study nr.	Pneumonia prevalence	Sensitivity	Specificity	PPV	NPV
Tachypnea	5 [1]	6.7%	74.27	42.05	8.44	95.78
	6.3 [2]	7%	77.78	60.18	13.46	97.14
Tachycardia	2	3.4%	63.04	57.36	4.91	97.80
	5	6.7%	50.29	57.28	7.81	94.12
Saturation <94%	5	6.7%	13.45	97.43	27.38	93.99
	6.3	7%	40.74	88.20	21.57	94.92
Wheezing	5	6.7%	15.38	93.87	8.06	96.95
	4	8.6%	20.45	83.69	10.59	91.76
Crackles	5	6.7%	35.83	92.64	14.54	97.64
	4	8.6%	20.45	86.48	12.50	92.01
Retractions	5	6.7%	14.62	92.51	12.32	93.77
	6.3	7%	29.63	89.38	18.18	94.10
	4	8.6%	31.82	71.24	9.46	91.71
Ill appearance	5	6.7%	30.99	80.01	10.04	94.16
	6.3	7%	77.78	81.42	25.00	97.87

Cut-of values for tachypnoea: [1]WHO definition [2]APLS criteria
Abbreviations:
PPV: positive predictive value, NPV: negative predictive value

Diagnostic value of laboratory tests

Four selected studies reported on the diagnostic value of laboratory tests in diagnosing pneumonia (Table 9). Three of these studies were designed to develop a clinical prediction model to identify children with a serious bacterial illness, including pneumonia (35,39,40). The clinical prediction models included additional laboratory tests. All four studies showed significantly higher values of CRP and mean white blood cell count in the presence of pneumonia. Other laboratory tests were only evaluated in one of the studies or evaluated using different units of measurements. All results are shown in Table 9. The diagnostic models, based first on signs and symptoms, improved when CRP (35,39), procalcitonin and resistin (40) were added. Data on specific cut-of points for the various laboratory tests, and corresponding univariate values for PPV and NPV were not available from any of the selected studies.

Table 9. Diagnostic value of laboratory tests for the diagnosis of pneumonia

Pneumonia prevalence	5. Nijman	13. Irwin	6.1 Oostenbrink	6.2 Oostenbrink	6.3 Oostenbrink	10. Urbankowska
	6.7%	11.4%	16%	14%	7%	72%
	Present vs. absent	Present vs absent	Present vs. absent	Present vs. absent	Present vs. absent	Present vs. absent
Mean CRP (mg/L)	47.5 vs 12.4					
Median CRP (mg/L)		49.0 vs 14.3*	86 vs 22*	109 vs 31*	61 vs 31*	1.95 vs 4.7*
Mean WBC (x10^9/L)			17.4 vs 12.8*	18.1 vs 12.7*	17.0 vs 19.1	
Median WBC (x10^9/L)		11.8 vs 10.8*				
Median WBC count (cells/microL)						10.1 vs 11.3
Median lymphocyte count (cells/microL)						3.6 vs 1.9*
Median neutrophil count (x10^9/L)		8.0 vs 6.2*				
Median neutrophil count (cells/microL)						4.3 vs 7.9*
NGAL (ng/L)		92.1 vs 69.7*				
PCT (µg/L)		0.49 vs 0.18*				
Resistin (ng/L)		67.3 vs 35.7*				

Abbreviations:
CRP: C-reactive protein WBC: white blood cell count NGAL: neutrophil gelatinase-associated lipocalin PCT: procalcitonin
* statistically significant difference

Diagnostic value of ultrasonography

Six selected studies reported on the diagnostic value of ultrasonography to diagnose pneumonia (Table 10). All these studies had a high prevalence of CXR confirmed pneumonia (range 18%-71.7%). Both PPV and NPV were high in most studies. However, one study found a much lower NPV ((41), Table 10). The authors of this paper attributed this difference with previous studies to a different study design with better blinding of the sonologist to the patients' clinical examination in their study, but also to the very basic training that pediatric residents received prior to performing the ultrasound examinations in this study.

Table 10. Diagnostic value of ultrasonography for the diagnosis of pneumonia

Nr.	Author	Pneumonia prevalence %	Sensitivity	Specificity	PPV	NPV
9	Shah	18	86.1	89.0	63.3	96.7
16	Samson	42.5	87.1	94.8	92.5	90.8
17	Zhan	50	40.2	91.5	82.5	60.5
15	Ianniello	56	97.9	64.9	77.9	96.0
14	Copetti	67	100	73.1	88.3	100
10	Urbankowska	71.7	93.4	100	100	85.7

Abbreviations:
PPV: positive predictive value, NPV: negative predictive value

DISCUSSION

Summary

This clinical systematic review aimed to summarize available evidence on the diagnostic value of relevant clinical information, such as physical signs, laboratory tests and ultrasonography in the assessment of children suspected of pneumonia in an ambulatory setting. We summarized the results of seventeen eligible studies. Overall, diagnosing pneumonia using individual signs and symptoms is not possible. Even established predicting signs of pneumonia, like crackles and tachypnoea score lower than usually presumed.

Although evidence for the diagnostic value of signs and symptoms in the low prevalence settings (prevalence of pneumonia <10%) is limited, clinically ill appearing children and the presence of saturation < 94% can support the primary care physician in ruling in pneumonia. In settings with a higher prevalence of pneumonia the presence of chest retractions, a saturation <94% and additional tests such as CRP and WBC count may further support an accurate diagnosis of pneumonia.

Ultrasonography seems promising given the high positive and negative predictive values in most of the studies that have evaluated this technique. However, quality assessment did reveal concerns with some of the studies. Specifically, we judged the risk of bias in the domain patient selection high or unclear in many of these studies (34,41–44). The high prevalence of pneumonia found in these studies is not representative of most ambulatory settings (table 3 and 4). This hampers generalizability, especially to settings with a lower prevalence of pneumonia. Furthermore, ultrasonography requires specific training. Authors describe that training can be basic, however one study that found a much lower NPV (41) attributed this partly to the inexperience with ultrasonography of the resident that performed the examination. Combined with the fact that ultrasonography currently may not be available to many physicians in primary or even secondary care makes that adoption of this new technique to ambulatory settings is not evident at this time.

Strengths and limitations

The field of primary care is evolving quickly, and aside from history taking and clinical examination, primary care physicians increasingly have access to additional diagnostic tools in, or close to, their practice. A strength of our review is that we took this development into account. We conducted a broad search and included all research in developed countries that was aimed at assessing the diagnostic value of history, physical examination and additional diagnostic tools at the point of care in an ambulatory setting. We specifically chose to only include diagnostic studies performed in developed countries, as we proposed children in developing countries may present with a different range of diseases and more advanced stage of disease at presentation. All search results were evaluated by two authors, to ensure that all eligible papers were included. Quality assessment was done systematically by two reviewers using the QUADAS-2. Although many studies showed some limitations, most often these limitations seemed inevitable given the chosen study designs or setting.

Our study also has several limitations. We chose to include only studies that used CXR as the golden standard for the diagnosis of pneumonia. Despite known limitations of CXR (23) it is still regarded as the reference standard for diagnosis in most studies and also in clinical practice (23,25). However, this inclusion criterium may have led to the fact that we found no studies performed in a primary care setting that fulfilled our inclusion criteria. The studies that we did identify were all conducted in ambulatory settings but still prevalence of pneumonia varied greatly. This may be due to differences in organization of health care in different countries. Where some countries offer direct access for patients to secondary care, other countries employ a gate-keeping system with primary care physicians controlling access to secondary care. Which system is used in a country, influences the prevalence of pneumonia in children in the secondary care settings. In turn, the prevalence of a disease, and thereby the pre-test probability of being ill or not, is highly relevant for the diagnostic value of a test. A different patient case-mix may lead to so called spectrum bias (45).

Most studies only included children who had an indication for a CXR. We scored these studies as high risk of bias in the domain patient selection during quality assessment. CXR is recommended only in children who might be admitted to hospital, and are more severely ill, by many guidelines (3,22,46,47). Ideally, when assessing the diagnostic value of a test for evaluating children in an ambulatory setting, a study should include all children presenting to a facility without this selection criterion. Only including children with an indication for CXR may mean that these children were at higher risk of actually having pneumonia. This may again bias the diagnostic performance measures (45).

Furthermore, this review evaluates diagnostic studies. A known limitation of many diagnostic studies is reproducibility, with known low inter-observer agreement between physicians when for example assessing auscultation. Whether reporting of signs and symptoms for a study was highly protocolized or not may also have influenced outcomes of individual studies.

We did not perform a meta-analysis in this review as included studies were too heterogeneous in setting, prevalence of pneumonia and study design to allow pooling of the found results. Rather, we chose to present all the extracted data on diagnostic values. Furthermore, we found no studies that fulfilled our inclusion criteria on the diagnostic value of laboratory tests alone for the diagnosis of pneumonia. So, although selected studies showed that CRP and WBC counts have diagnostic value, we are unable to calculate this exact value at different cut-off points. Prediction rules combining signs, symptoms and/or laboratory tests were not included in this review.

Comparison with other literature

Several systematic reviews have summarized the available evidence on the diagnosis of pneumonia in children. These reviews have all mainly focused on the objective to correctly identify the child that suffers from pneumonia. Rambaud-Althaus et al. (48) and Shah et al. (25) evaluated the diagnostic value of clinical features in younger children, also including children in low resource settings. Rambaud-Althaus et al (48) specifically examined studies in children younger than five years. Like in our review, both found large heterogeneity, and were unable to define one clinical feature for the diagnosis of pneumonia. Highest positive likelihood ratios were found for respiratory rate over 50 breaths per minute (48), hypoxemia and increased work of breathing (25). Shah et al. also found that tachypnoea has diagnostic value in excluding pneumonia. Both reviews stress the importance of combining the different features to make the diagnosis of pneumonia more or less likely, and recommend further investigation of these combinations, and possibly adding point-of-care tests. A systematic review by van den Bruel et al. (5) focused on clinical features to identify serious bacterial illness, including pneumonia, in children in developed countries. They found that respiratory rate was the most reliable sign in the diagnosis of pneumonia (positive likelihood ration 2.7-4.0 dependent on the cut-off point), but breathlessness and auscultatory signs did not have

high diagnostic values. Another systematic review by van den Bruel et al. looked specifically at the diagnostic value of laboratory tests in identifying children with serious infections, including pneumonia (26). They found that measuring CRP and procalcitonin provided most diagnostic value, and logically different cut-of points were necessary to either rule-in, or rule-out serious infection. Diagnostic value specifically for pneumonia was not available from this review. As in our review, the lack of studies in settings with low prevalence of serious infections is identified as a gap in the current evidence, as well as studies combining signs, symptoms and laboratory tests.

A recent review looking at the advances in the diagnosis of pneumonia by Zar et al. (23) summarizes some of the newer tests. Many of the described possible new biomarkers in this article, which mainly aim to differentiate between bacterial and viral infection, are at this stage far from being available as point-of-care tests in an ambulatory setting and therefore fall out of the scope of our article. However, they also describe the growing body of evidence on ultrasonography for the diagnosis of pneumonia, a technique that is already available using a point-of-care device. They conclude that although this new technique seems promising, the effect on clinical outcomes in patients warrants further investigation. We feel this is a very relevant recommendation, also supported by the results found in our review. Further research is also necessary in settings with a lower prevalence of pneumonia, to evaluate whether this technique holds possibility for adoption to such settings.

Implications for practice and further research

Not a single clinical sign or symptom has sufficient diagnostic value to adequately diagnose pneumonia in children, or safely rule it out. Dependent on the setting, the physician needs to combine multiple features to make the diagnosis more or less likely. When assessing the results, and applying them in practice, it is important that physicians are aware of the prevalence of pneumonia in their own setting and keep in mind that diagnostic value of tests may be different in their setting. The prevalence of pneumonia in the included studies in this review is stated in the different tables in our review, and studies with a lower prevalence of pneumonia (<10%) are presented separately from the studies with higher prevalence of pneumonia. Primary care physicians may evaluate the results presented for low prevalence settings but should be conscious of the fact that this evidence was derived from trials in secondary ambulatory care settings.

Future research should focus on the combination of clinical features and additional testing as the latter becomes more widely available. This can be done by designing new diagnostic trials but combining the already available evidence using the technique of meta-analysis of individual data may also increase our knowledge. In adults, this method has for example increased our knowledge of the added value of newer additional tests in ambulatory care like CRP (49).

There is a lack of evidence concerning the diagnosis of pneumonia in primary care settings, with low prevalence of pneumonia. More research should be conducted in this setting, as many children are evaluated in primary care, and a large proportion of the over prescription of antibiotics occurs in this setting (10–12). The role of additional tests such as point-of-care biomarkers or ultrasound should be subject of further evaluation leading to evidence that can help the primary care physician determine which children are in need of antibiotic treatment. In these settings, it is especially important for a physician to rule out pneumonia safely. This means the NPV of an index test is of major importance in this setting.

In conclusion, not a single item from history taking, physical examination or additional laboratory testing is sufficient to diagnose pneumonia in ambulant children and combining tests will be necessary to increase diagnostic certainty. Very few diagnostic studies are conducted in settings with low prevalence of pneumonia. Future research should focus on increasing evidence for these settings, and on synthesizing the evidence currently available. The addition of diagnostic tests seems promising for the future, but further evaluation is needed. Furthermore, clinical implications of additional diagnostic testing, including possibly performing ultrasound evaluation, also need careful evaluation.

METHODS

Search strategy

We performed a systematic search for articles reporting the diagnostic value of items from history and/or physical examination and/or additional diagnostic tests for diagnosing pneumonia. We searched the databases PubMed and Embase, without restriction in date of publication and language. Search terms included Mesh terms and free text terms on respiratory tract infection, pneumonia, clinical and laboratory test, infant or child and ambulatory care or primary care. Full search strategy is listed in Appendix 1. The first search was undertaken in November 2016 and was updated in November 2017. We checked reference lists of all retrieved articles. The study was registered with PROSPERO (50).

Study selection

Two independent reviewers performed selection. Selection was done in two rounds, first based on titles and abstracts (performed by WG and MS), and in the second round, based on the full text article (performed by AD and MS). In case of doubt or conflict a third reviewer (JC) was consulted.

Inclusion criteria for further evaluation are summarized in box 1. We only included studies on children age 0-12 years old. Pneumonia was defined as radiological confirmed pneumonia on chest X-ray (CXR). We only included index tests that currently available as point-of-care tests, or

have the possibility to soon be available as such a test, following the international consented definition for point-of-care tests primary care: 'a test to support clinical decision making, which is performed by a qualified member of the practice staff nearby the patient and on any part of the patient's body or its derivatives, during or very close to the time of consultation, to help the patient and physician to decide upon the best suited approach, and of which the results should be known at the time of the clinical decision making (51). Further specified inclusion criteria were formulated for study design, population and setting, reported outcomes and use of index tests and reference standard (Figure 1).

Box 1. Criteria for study selection

Design
Studies that prospectively assessed diagnostic accuracy were selected. Narrative reviews, letters, editorials, comments, and case series of less than 20 patients were excluded. Systematic reviews and meta-analyses were used only as a source of references.
Population
Studies needed to include children (0-12) with suspected pneumonia. If the study consisted only partially of children, results for children needed to be reported separately. Studies concerning only neonates were excluded.
Setting
Studies were performed in ambulatory setting in developed countries i.e. general practice, out-of-hours clinic, emergency room or the outpatient department of the hospital. Studies done in developing countries were excluded because of the different range of diseases and more advanced stage of disease at presentation. We used the United Nations list to define developed countries, which include Europe, Canada, the USA, Australia, New Zealand, and Japan.
Target disease and reference standard
Selected studies assessed the detection of community acquired pneumonia. Pneumonia was confirmed by chest X-ray.
Index test
Studies that assessed signs, symptoms, additional test and/or biomarkers to predict the presence of pneumonia were selected. Studies reporting on additional test and/or biomarkers were selected only if they were available in an ambulant setting or could become readily available in the near future.
Data reporting
Diagnostic value of signs, symptoms or additional tests was reported in the article or could be calculated from the data in the article

Quality assessment

The methodological quality of eligible full text articles was evaluated independently by two reviewers (AD and MS) using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (52). In case of doubt or disagreement a third reviewer was consulted (JC). In the assessment of risk of bias related to patient selection, we presumed the risk of bias to be high when only children who had a clinical indication for a CXR were selected for inclusion.

Data extraction

One author (MS) extracted the data. Study characteristics (year of publication, study setting, age of study population, percentage of children with pneumonia and total size of study population) use of reference test and index tests (definitions, procedures) were noted on predefined forms. All clinical evaluations and all laboratory tests or imaging techniques that are available for point of care testing, or may be available in ambulant care in the near future were considered as index tests and data on each index test were individually extracted per article. Signs and symptoms with different cut-off values were considered as separate index tests. Combinations of tests and clinical prediction rules were not considered in this review.

Analysis

From the raw data extracted from each study, we constructed two-by-two tables and calculated the relevant measures of diagnostic accuracy, i.e. sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each individual index test. When extracted data were insufficient to make these calculations, authors from the original studies were contacted and asked to provide more details. Given the aim of our study, results include both negative and positive predictive values. In a setting of low prevalence of pneumonia such as primary care, ruling out pneumonia is most relevant, making the NPV the more important diagnostic value of a test. In a setting such as an emergency care, both values may be of equal importance, but priority may be on ruling in pneumonia. This makes the PPV of the index test of higher importance.

Because of the wide range of pneumonia prevalence in different settings (25,48), diagnostic values of individual index tests are presented separately for studies with low prevalence of pneumonia (≤10%) and for studies with a high prevalence of pneumonia(>10%). With expected high heterogeneity between studies we planned meta-analysis if at least four studies with comparable inclusion criteria and comparable settings reported on an index test. After reviewing all included studies meta-analysis was not possible.

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Appendix 1. Full search criteria for PubMed and Embase

Search terms PubMed:
Concerning diagnosis:
"Respiratory Tract Infections"[Mesh] OR "pneumonia"[MeSH terms] OR Pneumonia/ OR Pneumonia, Bacterial/ OR (community-acquired pneumon*[tiab] or community acquired pneumon*[tiab])

Concerning diagnostic features:
"Signs and Symptoms"[MeSH] OR signs and symptoms OR "Fever"[MeSH] OR fever OR fast breathing OR tachypnea OR respiratory rate OR yale observation scale OR yale score OR yale scale OR Nelson score OR Nelson scale OR young infant observation scale OR "Tachycardia"[Mesh] OR fast heart rate OR "capillary refill time" OR clinical assessment*[tiab] OR clinical feature*[tiab] OR "predictive value of tests"[MeSH terms] OR "sensitivity and specificity"[MeSH terms] OR "reproducibility of results"[MeSH terms] OR "diagnostic test" OR "diagnostic tests" OR "physical examination"[MeSH terms] OR "medical history taking"[MeSH terms] OR "Clinical Laboratory Techniques"[Mesh]

Concerning the study population:
"infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms] OR paediatric [All fields] OR pediatric [All fields] OR "pediatrics" [MeSH term]

Concerning the study setting:
"Ambulatory Care"[Mesh] OR "Family Practice"[Mesh] OR general practice OR GP OR "Physicians, Family"[Mesh] OR "Primary Health Care"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR primary care

Search terms Embase:
Concerning diagnosis:
'pneumonia' OR 'lower respiratory tract infection' OR 'respiratory tract infection' OR 'respiratory tract infection'/exp OR 'infectious pneumonia'/exp OR 'lung infiltrate'/exp OR 'community acquired pneumonia'/exp

Concerning diagnostic features:
'diagnostic accuracy'/exp OR 'predictor variable'/exp OR 'breathing rate'/exp OR 'physical disease by body function'/exp OR (signs AND symptoms) OR 'fever'/exp OR fever OR 'fast breathing' OR tachypnoea OR 'respiratory rate' OR 'tachycardia'/exp OR 'fast heart rate' OR 'capillary refill' OR 'blood analysis' OR 'laboratory analysis' OR 'anamnesis'/exp OR 'blood examination'/exp OR 'examination'/exp OR 'respiratory tract examination'/exp OR 'vital sign'/exp OR 'lung auscultation'/exp OR 'diagnostic test'/exp OR'diagnostic value'/exp OR'diagnostic test accuracy study'/exp OR'diagnostic

value'/exp OR 'echography'/exp OR 'laboratory diagnosis'/exp OR 'physical examination'/exp OR 'symptom assessment'/exp

Concerning the study population:
'infant'/exp OR 'preschool child'/exp OR 'school child'/exp OR 'toddler'/exp OR 'adolescent'/exp OR 'pediatrics'/exp

Concerning the study setting
'ambulatory care'/exp OR 'general practice'/exp OR 'general practice' OR gp OR 'general practitioner'/exp OR 'family physician' OR 'primary medical care'/exp OR 'primary care' OR 'emergency ward'/exp

Appendix 2. Diagnostic value of signs & symptoms in a high prevalence population with CXR confirmed pneumonia

	Ayalon (2013)	Lynch (2004)	Oostenbrink (2013)	Oostenbrink (2013)	Rothrock (2001)	Shah (2010)	Shah (2013)	Urbankowska (2015	Wingerter 2012	Zukin (1986)
Pneumonia prevalence	181/525 (34%)	204/571 (35,70%)	Pop 1: 78/504 (16%)	Pop 2: 58/420 (14%)	67/329 (20%)	235/1622 (14.5%)	36/200 (18%)	76/106 (72%)	324/2008 (16.1%)	18/125 (14.4%)
Symptom										
Rhinorrhea										
	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV
	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV
	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity
	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity
Cough										
	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV
	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV
	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity
	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity
Emesis										
	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV
	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV
	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity
	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity
Diarrhea										
	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV	NPV
	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV	PPV
	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity	Specificity
	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity
Chills										
	NPV	64.51	70.58							90
	PPV	41.00	36.80							27
	Specificity	96.00	16.00							77
	Sensitivity	5.00	88.00							50
	NPV	63.60	72.73	66.84	65.47	66.80				
	PPV	32.73	37.17	38,03	34.00	54.84				
	Specificity	46.22	30.23	74.42	90.41	95.93				
	Sensitivity	49.72	78.45	29.83	9.39	9.39				

Appendix 2. continued

	Ayalon (2013)	Lynch (2004)	Oostenbrink (2013)	Oostenbrink (2013)	Rothrock (2001)	Shah (2010)	Shah (2013)	Urbankowska (2015	Wingerter 2012	Zukin (1986)
Pneumonia prevalence	181/525 (34%)	204/571 (35,70%)	Pop 1: 78/504 (16%)	Pop 2: 58/420 (14%)	67/329 (20%)	235/1622 (14.5%)	36/200 (18%)	76/106 (72%)	324/2008 (16.1%)	18/125 (14.4%)
Sensitivity	8.33	5.00								
Specificity	96.22	96.00								
PPV	53.57	41.00								
NPV	66.73	64.51								
Sensitivity		92.00								
Specificity		21.00								
PPV		39.30								
NPV		82.52								
Sensitivity		3.00								
Specificity		94.00								
PPV		21.75								
NPV		63.55								
Sensitivity		4.00								
Specificity		97.00								
PPV		42.57								
NPV		64.51								
	Weakness	Dyspnea	History of fever	Pleuritic pain	Wheeze	Sign				

Appendix 2. continued

	Ayalon (2013)	Lynch (2004)	Oostenbrink (2013)	Oostenbrink (2013)	Rothrock (2001)	Shah (2010)	Shah (2013)	Urbankowska (2015	Wingerter 2012	Zukin (1986)
Pneumonia prevalence	181/525 (34%)	204/571 (35,70%)	Pop 1: 78/504 (16%)	Pop 2: 58/420 (14%)	67/329 (20%)	235/1622 (14.5%)	36/200 (18%)	76/106 (72%)	324/2008 (16.1%)	18/125 (14.4%)
NPV	35.56	51								
PPV	77.33	60								
Specificity	22.65	13								
Sensitivity	84.09									
NPV	15.34									
PPV	0.57									
Specificity										
Sensitivity										
NPV	69.63	41								
PPV	45.07	68								
Specificity	77.33	60								
Sensitivity	35.56	51								
NPV	68.82	66								
PPV	53.95	60								
Specificity	89.83	95								
Sensitivity	22.65	13								
NPV	34.88									
PPV	31.42									
Specificity	4.44									
Sensitivity	84.09									
NPV	68.50									
PPV	65.85									
Specificity	95.86									
Sensitivity	15.34									
NPV	65.82									
PPV	50.00									
Specificity	99.70									
Sensitivity	0.57									
	>95% Oxygen saturation	90-95%	<90%							
	Tachycardia	Tachypnea								

Appendix 2. continued

	Ayalon (2013)	Lynch (2004)	Oostenbrink (2013)	Oostenbrink (2013)	Rothrock (2001)	Shah (2010)	Shah (2013)	Urbankowska (2015	Wingerter 2012	Zukin (1986)
Pneumonia prevalence	181/525 (34%)	204/571 (35,70%)	Pop 1: 78/504 (16%)	Pop 2: 58/420 (14%)	67/329 (20%)	235/1622 (14.5%)	36/200 (18%)	76/106 (72%)	324/2008 (16.1%)	18/125 (14.4%)
Sensitivity			14.10	32.76				3.90		6
Specificity			96.01	92.27				90.00		71
PPV			39.29	40.43				49.70		3
NPV			85.92	89.54				26.99		82
Sensitivity			33.33	79.31				2.60		78
Specificity			77.93	38.67				80.00		73
PPV			21.67	17.16				24.77		15
NPV			86.46	92.11				24.48		86
Sensitivity		56.02			23					57
Specificity		93.00			15					75
PPV		81.65			7					27
NPV		79.18			48					90
	<94%		Ill appearance		Rales		Wheezing		Rhonchi	

Appendix 2. continued

	Ayalon (2013)	Lynch (2004)	Oostenbrink (2013)	Oostenbrink (2013)	Rothrock (2001)	Shah (2010)	Shah (2013)	Urbankowska (2015	Wingerter 2012	Zukin (1986)
Pneumonia prevalence	181/525 (34%)	204/571 (35,70%)	Pop 1: 78/504 (16%)	Pop 2: 58/420 (14%)	67/329 (20%)	235/1622 (14.5%)	36/200 (18%)	76/106 (72%)	324/2008 (16.1%)	18/125 (14.4%)
		NPV								
		PPV								
		Specificity								
		Sensitivity								
Crackles		NPV	69.73					27.26		
		PPV	46.96					69.98		
		Specificity	73.00				75	60.00		
		Sensitivity	43.00				24	36.80		
Bronchial breathing		NPV	65.00					30.76		
		PPV	49.31					86.61		
		Specificity	96.00					93.30		
		Sensitivity	7.00					17.10		
Decreased breath sounds		NPV	68.26		20			35.97		
		PPV	40.01		2			83.37		
		Specificity	55.00		6		83	76.70		
		Sensitivity	54.00		9		24	46.10		
Retractions		NPV	64.98							
		PPV	58.15							
		Specificity	98.00							
		Sensitivity	5.00							
Grunting		NPV	64.74							
		PPV	100.00							
		Specificity	100.00							
		Sensitivity	2.00							

Appendix 2. continued

	Ayalon (2013)	Lynch (2004)	Oostenbrink (2013)	Oostenbrink (2013)	Rothrock (2001)	Shah (2010)	Shah (2013)	Urbankowska (2015	Wingerter 2012	Zukin (1986)
Pneumonia prevalence	181/525 (34%)	204/571 (35,70%)	Pop 1: 78/504 (16%)	Pop 2: 58/420 (14%)	67/329 (20%)	235/1622 (14.5%)	36/200 (18%)	76/106 (72%)	324/2008 (16.1%)	18/125 (14.4%)
Fever	Sensitivity Specificity PPV NPV	Sensitivity 47 Specificity 68 PPV 45 NPV 70	Sensitivity Specificity PPV 21.78 NPV 86.10	Sensitivity Specificity 83.43 PPV 35.48 NPV 92.35	Sensitivity 25 Specificity 18 PPV 7 NPV 48	Sensitivity Specificity PPV NPV	Sensitivity Specificity PPV NPV	Sensitivity Specificity PPV NPV	Sensitivity Specificity PPV NPV	Sensitivity 94 Specificity 36 PPV 20 NPV 97
Chest retractions/ nasal flare			Sensitivity 28.21 Specificity 81.46	Sensitivity 56.90 Specificity						
Respiratory distress										Sensitivity 17 Specificity 84 PPV 15 NPV 86

Cut-of values for tachypnoea: [1]WHO definition [2]APLS criteria [3]other

Abbreviations:

PPV: positive predictive value, NPV: negative predictive value, Pop: population

Appendix 3. Diagnostic value of signs & symptoms in a low prevalence population with CXR confirmed pneumonia

		Craig (2010)		Mahabee (2005)		Nijman (2013)		Oostenbrink (2013)	
		Pneumonia prevalence	3.4% (533/15781)	8.6% (44/510)		(6.7%) 171/2547		Pop 3 27/366 (7%)	
			Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Symptom																		
Cough			86.87	47.26	5.44	99.04												
Diarrhea			21.76	74.36	2.88	96.46												
Dyspnea/ difficult breathing			45.40	87.46	11.22	97.87												
Crying			37.15	67.13	3.80	96.84												

Appendix 3. continued

		Craig (2010)	Mahabee (2005)	Nijman (2013)	Oostenbrink (2013)	
		3.4% (533/15781)	8.6% (44/510)	(6.7%) 171/2547	Pop 3 27/366 (7%)	
Pneumonia prevalence	Sign					
	Tachycardia	NPV			97.14	94.92	97.87	
		PPV			13.46	21.57	25.00	
		Specificity			60.18	88.20	81.42	
		Sensitivity			77.78	40.74	77.78	
	Tachypnoea	NPV		94.12	95.78	93.99	94.16	
		PPV		7.81	8.44	27.38	10.04	
		Specificity		57.28	42.05	97.43	80.01	
		Sensitivity		50.29	74.27	13.45	30.99	
	<94% Oxygen saturation	NPV						
		PPV						
		Specificity						
		Sensitivity						
	Ill appearance	NPV		97.80				95.38
		PPV		4.91				1.56
		Specificity		57.36				58.38
		Sensitivity		63.04				18.95
	Well Ill appearance							

Appendix 3. continued

	Craig (2010)			Mahabee (2005)		Nijman (2013)		Oostenbrink (2013)	
Pneumonia prevalence	3.4% (533/15781)			8.6% (44/510)		(6.7%) 171/2547		Pop 3 27/366 (7%)	
NPV									
PPV									
Specificity									
Sensitivity									
NPV									
PPV									
Specificity									
Sensitivity									
NPV							91.76	92.01	
PPV							10.59	12.50	
Specificity							83.69	86.48	
Sensitivity							20.45	20.45	
NPV		96.91	97.19	96.71	96.95	97.64			
PPV		3.66	9.17	23.44	8.06	14.54			
Specificity		50.31	91.63	99.68	93.87	92.64			
Sensitivity		54.03	24.20	2.81	15.38	35.83			
		Mildly unwell	Moderately unwell	Very unwell					
					Wheezing	Crackles			

Appendix 3. continued

		Craig (2010)		Mahabee (2005)		Nijman (2013)		Oostenbrink (2013)	
	Pneumonia prevalence	3.4% (533/15781)		8.6% (44/510)		(6.7%) 171/2547		Pop 3 27/366 (7%)	
			NPV						
			PPV						
			Specificity						
			Sensitivity						
			NPV						93.32
			PPV						7.61
			Specificity						96.42
			Sensitivity						4.09
			NPV	91.89					
			PPV	17.24					
			Specificity	94.85					
			Sensitivity	11.36					
			NPV		98.17	96.28	96.89		
			PPV		11.60	1.73	8.91		
			Specificity		85.70	82.12	95.72		
			Sensitivity		54.03	9.01	12.01		
				Decreased breath sounds	Abnormal chest sounds	Rash	Capp refill >2sec	Capp refill >3sec	

Appendix 3. continued

	Craig (2010)	Mahabee (2005)	Nijman (2013)	Oostenbrink (2013)
Pneumonia prevalence	3.4% (533/15781)	8.6% (44/510)	(6.7%) 171/2547	Pop 3 27/366 (7%)
				NPV
				PPV
				Specificity
				Sensitivity
				NPV
				PPV
				Specificity
				Sensitivity
			NPV	
			PPV	
			Specificity	
			Sensitivity	
		NPV		
		PPV		
		Specificity		
		Sensitivity		
	Temperature ³38°C	Temperature ³39°C	Nasal flaring	Grunting	Retractions
	97.30	97.36			
	3.56	4.36			
	21.95	57.89			
	82.55	54.97			
			92.67	91.22	91.71
			21.74	5.00	9.46
			92.27	95.92	71.24
			22.73	2.27	31.82
					94.10
					18.18
					89.38
					29.63
					93.77
					12.32
					92.51
					14.62

Appendix 4. Diagnostic value of ultrasonography

		Shah (2013)	Samson (2018)	Zhan (2016)	Urbankowksa (2015)	Ianniello (2015)	Copetti (2008)		
% Final diagnosis pneumonia		36/200 (18%)	85/200 (42.5%)	82/164 (50%)	76/106 (71.7%)	47/84 (56%)	53/79 (67%)		
Point-of-care ultrasonography	NPV	96.69	90.8	60.5	85.7	96.00	100.00		
	PPV	63.27	92.5	82.5	100	77.97	88.33		
	Specificity	89.02	94.8	91.5	100	64.86	73.08		
	Sensitivity	86.11	87.1	40.2	93.4	97.87	100.00		
> 1cm lung consolidation on ultrasonography	NPV	97							
	PPV	86							
Right chest	Specificity			88					
	Sensitivity			49					
Left chest	Specificity			95					
	Sensitivity			33					

CHAPTER 4

C-reactive protein point-of-care testing in children with cough; qualitative study of GPs' perceptions

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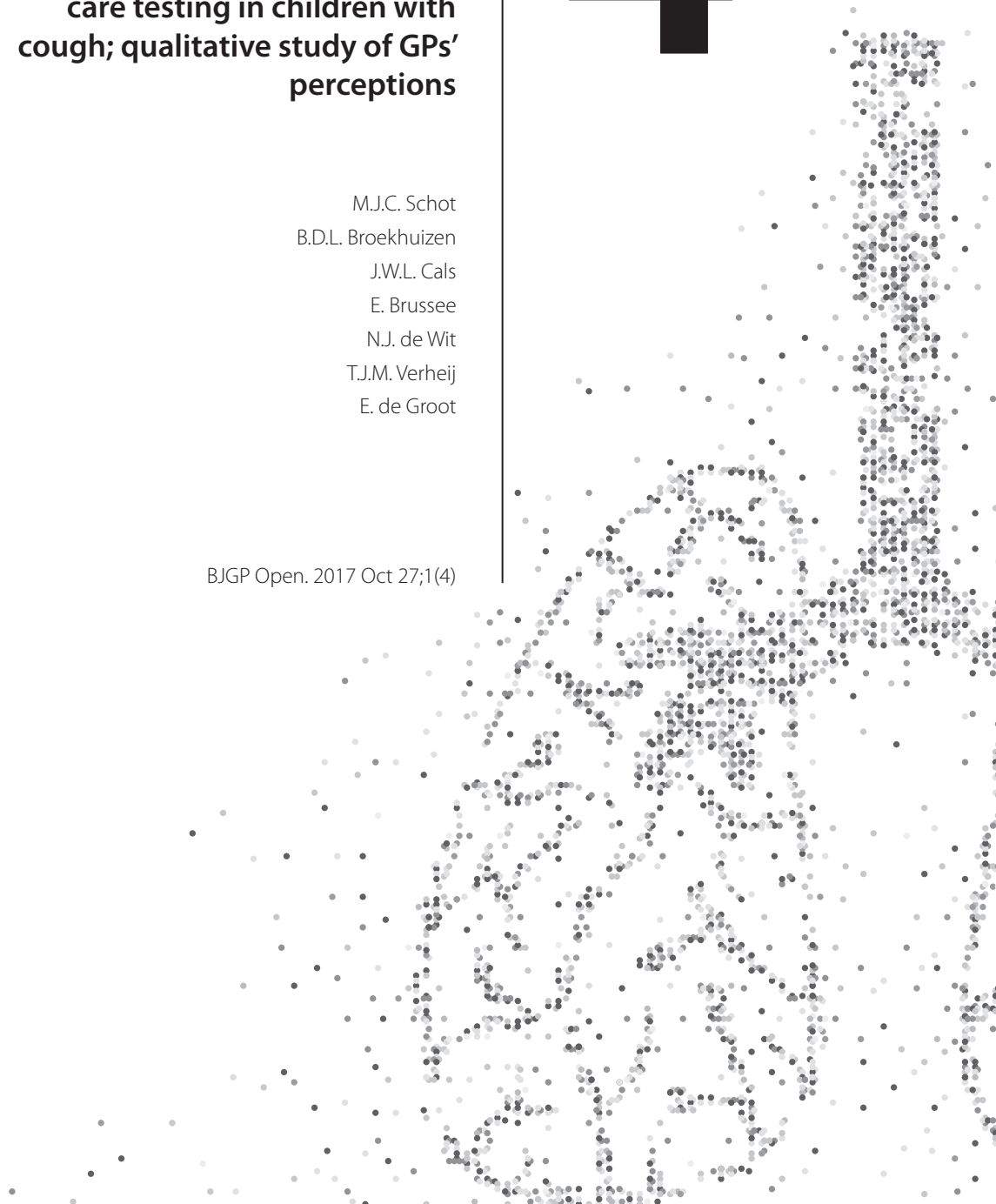

ABSTRACT

Background

Point-of- care CRP testing is widely accepted in Dutch general practice for adult patients with acute cough, but GPs' perceptions of its use in children with LRTI are unknown. Knowledge of these perceptions is important when considering broadening its indication to use in children.

Aim

To explore the perceptions of Dutch GPs of the addition of point-of-care CRP testing to the diagnostic evaluation of children, and compare these to their perceptions of use in adults.
Design and setting. Qualitative study in general practice.

Methods

Semi-structured interviews were held with eleven GPs. Interviews were analysed using open coding and a thematic approach.

Results

GPs' perceptions of the addition of point-of-care CRP testing in children with suspected LRTI differ from their perceptions of this in adults. We identified five themes: patient characteristics: vulnarability of the child, clinical presentation, availability of evidence, impact of the procedure and use of point-of-care CRP testing as a communication tool.

Conclusion

Differences between the perceptions of using point-of-care CRP testing in children and adults need to be addressed when considering the possible implementation of this diagnostic instrument.

INTRODUCTION

Point-of-care testing (POCT) C-reactive protein (CRP) has proven to safely reduce antibiotic prescriptions for adults with acute cough (1) and has been incorporated in the NICE guideline on community-acquired pneumonia (2) and in the Dutch primary care practice guideline (3). Acute infections in children are common, with acute respiratory tract infection being the most common diagnosis in primary care. Lower respiratory tract infection (LRTI) has an annual incidence of 34,3 per 1000 children (4). In children, antibiotic overprescription is a problem, as in adults, with inappropriate prescribing occurring in 32% of consultations for children with lower respiratory tract infection (5). Whether the use of POCT CRP for children with suspected LRTI is effective in safely reducing antibiotic prescriptions is currently under investigation. National guidelines discourage its use in children until further research provides evidence on its clinical value (3). If proven effective, knowledge of GPs' perceptions of the addition of POCT CRP in children with acute cough is essential as uptake of a new diagnostic instrument is highly dependent on perceptions of users (6,7). Though sometimes overlooked, this aspect may be as important as an assessment of the effectiveness of the diagnostic intervention itself.

Qualitative studies show that for adult patients, POCT CRP enhances patients' and GPs' confidence in prescribing decisions as it supports the diagnostic and therapeutic process and helps GPs to manage patients' expectations for antibiotic treatment for LRTI (8,9). Disadvantages mentioned are difficulties with the interpretation of test results and possible distraction from clinical reasoning when using a diagnostic device (9). One pilot study evaluated the acceptability and usability of POCT CRP in children and found that parents would likely accept the test, but the five interviewed GPs were divided on the utility of the diagnostic test (10).

Currently half of the Dutch general practitioners (GPs) and 15% of UK GPs have POCT CRP available in their practice (11). How GPs with ready access to and experience with POCT CRP in adults view the possible introduction of this test in children is unknown. There are, however, reasons to believe that their evaluation might be different, as children are considered a vulnerable group of patients (12).

We aim to understand why GPs in the Netherlands would decide (not) to include POCT CRP measurement in the diagnostic process in children with LRTI, especially in comparison to their perceptions of using POCT CRP in adults. We, therefore, aim to answer the following research question: do GPs' perceptions of the use of POCT CRP in the diagnostic evaluation of children with LRTI differ from their perceptions of the use of this test in adults, and if so in what respect?

METHODS

This qualitative study was performed as part of a broader research program which also includes an ongoing pragmatic randomized controlled trial concerning the effect of POCT CRP measurement in children with suspicion of LRTI on antibiotic prescriptions (PRICE, Dutch trial registration code 4399). In this trial, GPs in the intervention arm are instructed to use POCT CRP when they experience diagnostic uncertainty in children with suspected LRTI.

GPs were approached to participate in this study first based on convenience sampling: three GPs from our clinical network and three GPs with varying clinical experience participating in our trial were interviewed. Thereafter we applied purposive sampling to recruit other GPs to ensure that we incorporated views of GPs who were known advocates and opponents of the introduction of POCT CRP in adults, academic GPs, and GPs with differing subject relevant clinical experience. Participants provided written informed consent to participate in this study. The Act on Medical Research involving human subjects did not apply to this study and therefore an official approval of this study by the Medical Ethics Research Council of the University Medical Center Utrecht was not required.
We interviewed participants face to face in their own surgery using a topic guide (table 1). Interviews were centered around the following topics: the GP's opinion on the use of POCT CRP in children with LRTI, the factors influencing the GP's decision to add POCT CRP to the diagnostic evaluation of children and the possible consequences of the use of POCT CRP in children with LRTI. The topics functioned as a guide during the interviews without being restrictive and thus allowing flexibility to explore emerging themes. As data collection and analysis were carried out iteratively, the topic guide was adapted as the interview process progressed based on new insights gained. The same interviewer (EB) conducted all interviews . Interviews took place between January and May 2015, lasted about 30 minutes, were fully audio-recorded and transcribed verbatim before analysis. As a member check, a summary of the interviews was sent to the GPs, but this did not lead to adjustment of any of the transcriptions. When after convenience, and later purposive sampling, no new perceptions were voiced and no new codes emerged during analysis, we decided that data saturation had been reached and stopped conducting additional interviews.

The anonymized transcripts were analysed in five steps: familiarization, open coding, creation and revision of (sub)categories, abstraction and interpretation (13). Familiarization started with reading each interview at least once. Transcripts were then reread and coded where they contained concepts related to our research question. When new codes emerged during the process, preceding transcripts were reread and recoded where needed. Subsequently, categories and subcategories were derived from our initial coding. Abstraction implied the generation of main categories by grouping subcategories together as much as possible. Eventually, results were interpreted into themes to formulate an answer to our research question.

The study team consisted of researchers with different backgrounds. EG has a background in the learning sciences, all other researchers have a background in primary care research and work in general practice. All researchers who did the analysis have experience with qualitative research. The different backgrounds allowed complementary views on the collected data. Reliability was endorsed by coding all data by two researchers (EB, MS). Discrepancies in coding or interpretation were resolved through discussion. Categories were set up after discussion and agreement between researchers (MS, EG, LB, JC). All interview transcripts were managed and analysed using NVivo 10.0.

Table 1. Topic guide for interviews with general practitioners

1.	What is your opinion on the use of POC CRP in children with LRTI in primary care?
2.	Which factors influence you in your decision (not) to add POC CRP to the diagnostic evaluation of children with LRTI?
3.	What are, according to you, possible consequences of the use of POC CRP in children with LRTI in primary care?

RESULTS

Characteristics of respondents

Eleven GPs from nine general practices participated. All participants had experience with CRP as a laboratory biomarker, eight participants had access to POCT CRP in their practice, and three GPs were participating in the ongoing randomized clinical trial. Most GPs used POCT in adults regularly. Only one GP did not use CRP measurement in the diagnostic process of LRTI in adults. GPs mentioned that they never or rarely used POCT CRP in children. Even the three GPs that were involved in the trial indicated they rarely used the test in children.

GPs mentioned multiple differences between adults and children concerning the possible addition of POCT CRP in a diagnostic process. We identified five themes in our data: patient characteristics, clinical presentation, availability of evidence, impact of the procedure and use of POCT CRP as a tool for communication.

Patient characteristics: vulnerability of the child

GPs mentioned considering children as more vulnerable than adult patients. This was illustrated in several ways: they mentioned their fear of unpredictable and faster deterioration in children with LRTI, but also feared that in case of such a sudden deterioration, this might not be noticed timely by some parents. Many mentioned not wanting to miss a serious infection or risk complications specifically in children.

'In adults…at least they feel it themselves, it's their own body, and they will call again if necessary. An adult can also stand more. But a small child…yes, it can also change very quickly. And in adults, you just don't see that very often.' GP11

'Young children are more vulnerable than adults, for whom you can use watchful waiting…in adults it's easier to say: 'we will wait and if you don't improve in a day or two you can come back'…In children, this is possible too, but you're more cautious. You don't want to take the risk that the child deteriorates and that, that it could have been prevented with antibiotics.' GP10

GPs mentioned being more cautious, leading to quicker antibiotic prescription for children than for adults. This cautious approach also influenced their appraisal of POCT CRP. Several GPs stated that they would not have their judgment affected by a low POCT CRP test result in the case of diagnostic uncertainty in children, as they would in adults.

'In children, I might be a bit more cautious, so then I tend to prescribe antibiotics, yes, when in doubt, and skip the POCT CRP.' GP2

Clinical presentation

Patients are evaluated based on history and physical examination by a GP. GPs agreed that presentation of symptoms could be quite different in adults as compared to children. Most mentioned that even though history taking is more difficult in children, assessment of the severity of their disease is more straightforward than with adults.

'And you know, a child is, I would almost say, purer in a sense. A child feels ill or it doesn't and you can see that. An adult can make all sort of theatre around this and, yes, sometimes you will then think 'ehm..' it is not that bad. Or the other way around.' GP1

It seemed that GPs less often felt uncertain about their judgement of a child than of an adult, what led them to conclude that the addition of POCT CRP was not needed.

Availability of evidence

GPs mentioned another obstacle in using POCT CRP in children. Whereas the use in adults is recommended by professional guidelines, two GPs specifically mentioned that since guidelines currently do not recommend the use in children, this withheld them from using the test. Others mentioned that they considered the present level of evidence for using POCT CRP in children insufficient to justify adding it to the diagnostic process. A majority mentioned they had difficulty with the interpretation of test results and were unsure of optimal cut-off values for children. They specified that it was unclear whether the cut-off values that were recommended by guidelines for adults could also be applied to children. Some mentioned that because of this lack of clarity on cut-off-values and lack of evidence with

regard to the trustworthiness they valued their clinical judgement over the CRP values, which led them to skip CRP measurement or decide to prescribe antibiotics even when CRP values were low.

'I just don't know what the normal range is…you know, in adults we stick to 20 and 100, that is the range, those are the limits. And I don't know whether those values also apply in children.' GP4
'At this stage, there is no clear evidence that POCT CRP is a useful tool in children, so, I actually don't use it at all.' GP8

Impact of the procedure

The majority of GPs considered the required finger prick to collect the blood sample for testing to be invasive. They were reluctant to hurt or scare their young patients, or cause fear for future consultations. In contrast, in adults, the blood sampling procedure itself was not a reason to refrain from POCT CRP. GPs expressed they could easily explain the necessity of the test and the required finger prick to adults, whereas children often would not understand this explanation.

'…I try to perform as few painful examinations in children as possible to avoid children being scared during future visits to my surgery. I would really like to keep a good relationship with the child and by performing painful pricks well…it can create reluctance during future consultations, this in contrast to adults where you can easily explain and this is not an issue' GP5

Use of POCT CRP as a communication tool

GPs noted that they not only used POCT CRP in adults in case of their diagnostic uncertainty, but also as a tool to communicate a non-prescription decision. GPs indicated they seldom used POCT CRP in children to convince parents that antibiotics were not necessary. Many pointed out that in their perception, parents quite often had reservations about giving their children antibiotics, whereas GPs often felt pressure from adult patients to prescribe. However, some GPs did mention there might be situations, although rare, in which POCT CRP could be used in children to reassure parents that antibiotics are not necessary.

'If parents are really worried, but after physical examination, I myself am reassured, I will try to explain this to the parents. In one case I did use POCT CRP because I could not reassure the parents. (…) This is an exception. I actually never use it, in children, for this reason.' GP 2

The three GPs without access to POCT CRP had similar arguments against the use of POCT CRP in children as those who did have access to the test. However, they were more outspoken in their perceptions. They also stressed the importance of clinical assessment over the use of additional tests and indicated that they felt it would never influence their clinical judgement and would not change their antibiotic prescription policy. All three pointed out that the current level of evidence had not convinced them POCT CRP would have additional value in children. In contrast to the other GPs, two of them felt this also to be true for adults.

DISCUSSION

Summary of main results

In a primary care setting in which most GPs have access to and experience with POCT CRP, GPs' perceptions of adding POCT CRP to the diagnostic process of LRTI in children are quite different from their perceptions for adults. While GPs feel that POCT CRP is helpful in managing adults with a cough in case of diagnostic uncertainty and in communicating about their decision not to prescribe antibiotics, they are quite reluctant to add POCT CRP to the diagnostic evaluation of children with LRTI. Themes we identified are the vulnerability of a child as a patient and the differences in clinical presentation between children and adults. Furthermore, the lack of evidence for the use of POCT CRP in children was a theme, as was the invasiveness of the diagnostic test. The last theme was the use of POCT CRP as a tool for communicating, which was also viewed differently for children.

GPs express that their current management of children with LRTI is primarily based on an assessment of clinical symptoms and characterised by a more cautious approach than in adults, where they are less inclined to watchful waiting. Specifically, and in contrast with adult patients, GPs fear fast and unexpected clinical deterioration of symptoms in children, which makes them apply a 'better safe than sorry' approach in prescribing decisions. They value reduction of diagnostic uncertainty by POCT CRP as less important in children than in adults. In combination with uncertainty towards the exact diagnostic value of POCT CRP and usable cut-off values, this leads to reservations on implementation of POCT CRP for children.
Various GPs mention they frequently use POCT CRP in adults to convince patients about the low severity of disease and to support their non-prescribing decisions. GPs express that they do not need this in children, as they feel less pressured by parents to prescribe antibiotics, and parents understand non-prescribing decisions.

Strengths and limitations

This study is the first in-depth qualitative study exploring GPs' perceptions of POCT CRP in children with LRTI in a setting where most GPs have access to and experience with this diagnostic instrument. The chosen sampling strategy enabled us to explore and compare GPs' perceptions considering the research topic. Double coding of all transcripts and member checks secured reliability. An inductive approach, with the addition of interviews until data saturation, allowed themes to emerge from the data rather than being established before data collection and analysis.

The perceptions of Dutch GPs interviewed in this study do not necessarily mirror those of GPs in other countries as country-specific health systems and cultural factors may influence GPs' perceptions of the implementation of tests such as POCT CRP. However, in earlier studies,

GPs' perceptions of the implementation of POCT CRP for adults did not differ much across countries with a strong primary care system (9,11,14).

Comparison with existing literature

As far as we know, only one mixed methods study previously investigated the acceptability and usability of POCT CRP in children in a primary care setting in the UK (10). However, the five participating GPs in that study had little or no experience with this diagnostic instrument. Acceptability was evaluated in parents, but not in GPs, as the finger prick was carried out before clinical assessment of the child. GPs were only asked if they found the addition of POCT CRP to their evaluation usable. This is a distinctly different procedure than the current practice in the Netherlands, where additional testing is only applied after clinical evaluation. The procedure of carrying out the finger prick before examination by the GP probably led to the fact that the reluctance to perform a finger prick by GPs found in our study as barrier for the use of POCT CRP, is not a theme in the UK-based study, The need for more evidence and guidance clear regarding the diagnostic value of POCT CRP in children is a theme found in both studies.

It is known that medical professionals view children as a vulnerable group (12) and that these beliefs, combined with perceived uncertainty in identifying children with a potentially serious bacterial infection, influence their prescribing decisions (15). A recent systematic review of qualitative studies examined views of clinicians on prescribing decisions in children (16). Clinicians reported prescribing antibiotics to children with acute infections 'just in case' when they were not confident about the diagnosis or about possible social, health or legal consequences of not prescribing. Doubts about whether parents could safely monitor the illness, especially when patients were not familiar to the physician, was also reported to drive the prescription of antibiotics. Our study aligned with this overall perception of children as a vulnerable group, with GPs not wanting to take the risk of a child deteriorating, and their uncertainty about the parental role in the follow-up of children.

Implications for practice and further research

Whether POCT CRP can increase the diagnostic certainty of GPs and help to identify children that need antibiotics and those who do not is still under investigation. However, uptake of a diagnostic instrument and the impact of the test results on management depend on the individual GP (17). Therefore, it is important to elaborate further on our result that GPs reported less diagnostic uncertainty in children, as this seems to be one of the reasons that GPs in our study considered additional (invasive) diagnostic tests less required for the evaluation of children in comparison to adults.

CONCLUSION

GPs' perceptions of the use of POCT CRP in children differ from those of the use in adults with suspected LRTI. Uncertainty about the exact role of POCT CRP and relevant cut-off values, in combination with the perception of a child as a vulnerable patient, causes GPs to refrain from using the test at present. If POCT CRP proves to be useful in safely reducing antibiotic prescription in children, it is crucial for successful implementation that these perceptions are taken into account.

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CHAPTER 5

Point-of-care C-reactive protein to assist in primary care management of children with suspected non-serious lower respiratory tract infection; a randomized controlled trial

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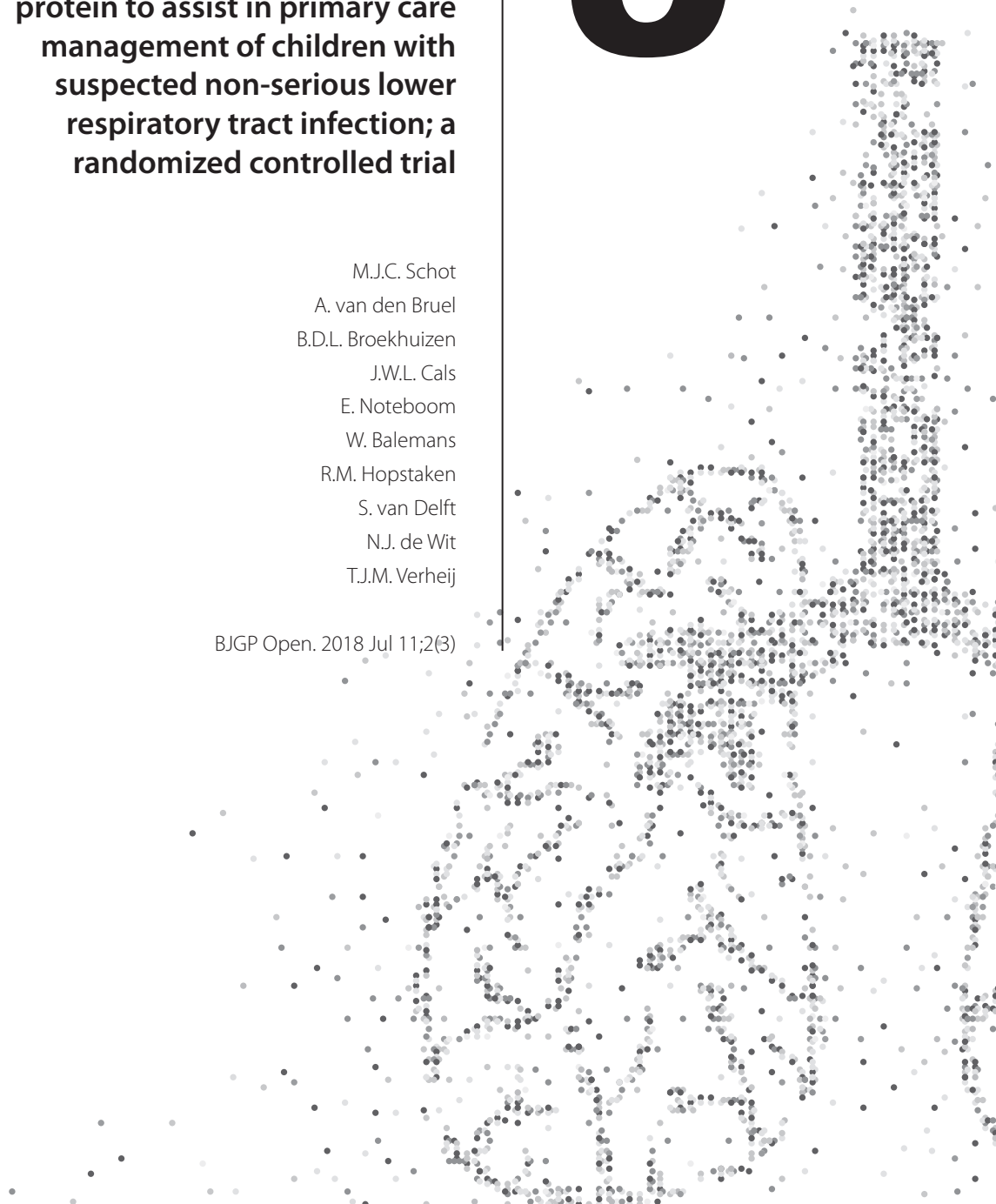


ABSTRACT

Background

Overprescription of antibiotics for lower respiratory tract infections in children is common, partly due to diagnostic uncertainty, in which case addition of point-of-care C-reactive protein testing can be of aid.

Aim

To assess whether use of point-of-care CRP by the general practitioner reduces antibiotic prescriptions in children with suspected non-serious lower respiratory tract infection.

Design and setting

Open, pragmatic, randomized controlled trial in daytime general practice and out-of-hours services. Methods: Children between 3 months and 12 years of age with acute cough and fever were included and randomized to either use of point-of-care CRP or usual care. Antibiotic prescription rates were measured and compared between groups using generalizing estimating equations.

Results

We found no statistically significant reduction in antibiotic prescriptions in the GP use of CRP group (30.9% vs. 39.4%; OR 0.61; 95CI 0.29-1.23). Only the estimated severity of illness was related to antibiotic prescription. 46% Of children had point-of-care CRP levels below 10mg/L.

Conclusions

It is still uncertain whether point-of-care CRP measurement in children with non-serious respiratory tract infection presenting to general practice can reduce the prescription of antibiotics. Until new research provides further evidence, point-of-care CRP measurement in these children is not recommended.

INTRODUCTION

Acute respiratory tract infections are the most common diagnoses in children in primary care (1, 2). Childhood lower respiratory tract infections (LRTI) include acute bronchitis, bronchiolitis and pneumonia. Pneumonia is a rare but serious condition and should be treated with antibiotics because of the difficulty in distinguishing viral from bacterial causes (3, 4), whereas bronchitis and bronchiolitis are more common and usually self-limiting illnesses (5-7).

Despite being of value in only a minority of children with LRTI, and contrary to recommendations in national guidelines (4), antibiotics are frequently prescribed in general practice in the Netherlands, with prescription rates varying between 56 and 70% (1, 8, 9). Diagnostic uncertainty, parental worries and expectations, or the general practioner's (GP's) anticipation of these, are important drivers of antibiotic prescriptions (8, 10, 11). Even in a low prescribing country like the Netherlands, 48-63% of antibiotic prescriptions are thought to be inappropriate (10, 12). This is harmful as antibiotics cause side effects (13), increase re-consultation rates (14) and contribute to antimicrobial resistance. Repeated use of antibiotics increases antimicrobial resistance in communities, but also in individuals (15, 16) making it important to correctly identify children who need antibiotics, but equally important to protect those who will not benefit.

Although CRP levels do not allow differentiation between bacterial or viral origin of an infection in adults or children, they are proxy for the disease severity (17-19). In adults, point-of-care C-Reactive Protein (CRP) has added value in the diagnosis of pneumonia (20-22) and safely reduces antibiotic prescriptions for acute respiratory tract infections in primary care (23). Following this evidence, national guidelines on acute cough recommend point-of-care CRP testing for adults in case of diagnostic uncertainty (4), similar to the current NICE guideline on pneumonia in adults (24). More than half of all Dutch GPs now have access to point-of-care CRP testing, in daytime practice as well as at out-of-hours services (25, 26).

Although point-of-care CRP is also of diagnostic value for diagnosing pneumonia in children (27) and useful in ruling out serious infection in children (28), its effect on antibiotic prescribing for children with symptoms of LRTI is unclear. In this study, we assessed whether point-of-care CRP testing in children with a suspected non-serious LRTI reduces antibiotic prescribing compared to usual care without CRP testing.

METHOD

This is a pragmatic, open, randomized controlled two-arm trial in primary care.

Participants and setting

Between December 2013 and May 2016, children aged between 3 months and 12 years were recruited in 28 daytime general practices across three different regions in the Netherlands. Due to slow recruitment rates children were additionally recruited at four out-of-hours services between November 2015 and May 2016. Children were eligible for inclusion if they had acute cough, reported fever, and were suspected of having a non-serious LRTI by the treating GP. Children who were judged as severely ill or highly suspect of pneumonia were excluded (table 1). Parents provided written informed consent.

Table 1. Eligibility criteria

Inclusion (all criteria must be present)	Exclusion (any presence of)
Suspicion of LRTI	Impaired immunity
Age 3 months – 12 years	Severe pulmonary disease
Acute cough < 21 days	Serious congenital defects
Reported fever >38 °C, < 5 days	Use of systemic antibiotics and/or corticosteroids in past 4 weeks
	Judged severely ill by the GP based on symptoms and signs
	Highly suspected of having pneumonia by the GP
	Referral to specialist or emergency department deemed necessary by GP

Randomization

Daytime general practices were cluster randomized per practice, to avoid contamination. Furthermore, we expected GPs might experience a learning effect from conducting CRP tests. By linking CRP levels to apparent severity of illness, this could have affected prescribing in the control group. We used block randomization stratified by region and practice type (academic vs. non-academic) (29).

Arguments for cluster randomization were not applicable to an out-of-hours service, where GPs participated in our study during one shift, and included two children at most. Therefore, children recruited at out-of-hours services were individually randomized using sequentially numbered opaque sealed envelopes (SNOSE) (30). The SNOSE piles were prepared by a member of the research team, using permuted block randomization. After the treating GP checked eligibility, an on-site research assistant, blinded to the clinical evaluation of the child, opened the envelope.

Intervention

For children in the intervention group a point-of-care CRP test was performed after clinical assessment by the treating GP. In the control group GPs were advised not to use point-of-care CRP, and treatment decisions were based on clinical assessment as usual.

CRP was measured using an Afinion® point-of-care testing device (Alere Technologies AS, Oslo, Norway), with a measurement range between 5 and 160 mg/L, and reliable for use in children (31). The result of the test is available within four minutes, requiring 1,5µL of blood obtained via finger prick.

GPs were not provided with strict decision rules based on CRP levels, but were given the following guidance:

1. Point-of-care CRP levels should be interpreted in combination with symptoms and signs.
2. CRP levels < 10mg/L make pneumonia less likely, but should not be used to exclude pneumonia when the GP finds the child ill, or when duration of symptoms is less than 6 hours.
3. CRP levels > 100mg/L make pneumonia much more likely, however, such levels can also be caused by viral infections.
4. Between 10mg/L and 100mg/L the likelihood of pneumonia increases with increasing CRP levels.

All management decisions including the use of other diagnostic tests and treatment were left to the GP's discretion.

Data collection

At baseline, GPs recorded the child's temperature and assessed illness severity on a Visual Analogue Scale. At the end of consultation, they registered their working diagnosis and treatment plan. Three months after inclusion, children's' medical records were reviewed to collect data on secondary outcomes.

Outcomes

The primary outcome was antibiotic prescribing at the index consultation. Secondary outcomes were re-consultation and antibiotic prescribing during the same illness episode, consultation for a new episode of any respiratory tract infection within three months of the index consultation and antibiotic prescriptions at these consultations.

Sample size calculation

Sample size calculation was based on the expectation that point-of-care CRP testing would reduce antibiotic prescribing by at least 20%, from 70% to 50%. To detect such a difference with 80% power and two-sided 5% significance, and considering a cluster size of 16 and an intra-cluster (intra-family practice) correlation coefficient of 0.06, a total of 354 patients were required. After expanding recruitment to the out-of-hours services we did not alter our sample size calculations as a cluster effect is not present for the children individually randomized at the out-of-hours services and this would most likely lead to a reduction in the number of children needed.

Statistical analysis

For the primary outcome, we analysed data with an intention to treat approach using general estimating equations to account for cluster effects and the baseline characteristics age, estimated illness severity, inclusion at out-of-hours service, and index of deprivation based on postal code. Children with missing outcomes were excluded from the analysis. Additionally, we analysed the primary outcome using a per protocol approach. Secondary outcomes are analysed using generalized estimating equations to account for cluster effects. Analysis was done using SPSS 21.

RESULTS

309 Children were recruited by 148 GPs, 210 children at general practices and 99 at an out-of-hours service (figure 1). Eight children were excluded due to missing age (n=7) or severity of illness score (n=1) at baseline. Characteristics of children in both groups were similar regarding age, sex, symptoms, fever, and estimated illness severity. In the control group, more children had a low social economic status (Table 2). GPs noted bronchitis as their final diagnosis in 21.3% of the children, and pneumonia in 13.3%. Significantly more children were diagnosed with an upper respiratory tract infection in the intervention group, and significantly more children were diagnosed with bronchitis in the control group. All diagnoses are listed in table 3. Based on estimated illness severity, children presenting to the out-of-hours service were not more severely ill than children presenting to daytime general practice (mean VAS score 3.7 SD 2.1 vs. 4.0 SD 1.8).

Table 2. Characteristics of randomized children at baseline

	GP use of CRP (N=136)	Control (N=165)
Median age (range)	3 (0-11)	2 (0-11)
Female sex	65 (47.8%)	81 (49.1%)
Abnormalities at auscultation	71 (50.4%)	83 (49.4%)
Signs of OMA	13 (9.2%)	23 (13.7%)
Signs of tonsillitis	17 (12.1%)	18 (10.7%)
Mean temperature (°C)	38.2	38.0
Estimated severity of illness by GP mean (SD)	4.0 (2.0)	3.8 (1.8)
Recruited at OOH service	49 (36%)	49 (29.7%)
Low social economic status	4 (2.9%)	17 (10.3%)

OOH service: out-of-hours service

Antibiotic prescription and re-consultations

GPs in the CRP group prescribed antibiotics to 30.9% of the children compared to 39.4% in the control group (OR 0.61; 95%CI 0.30-1.24). The only factor significantly related to the prescription of antibiotics was the estimated illness severity (OR 1.44 95%CI 1.26-1.66).

Table 3. Recorded diagnosis by GP after medical history, physical examination and point-of-care CRP if applicable

	GP use of CRP		Control group		
Diagnosis	N	%	N	%	P-value
Upper respiratory tract infection	62	45.6	47	28.5	0.002
Bronchitis	23	16.9	44	26.7	0.029
Pneumonia	16	11.8	22	13.3	0.683
Cough	11	8.1	16	9.7	0.627
Respiratory tract infection, not specified	6	4.4	3	1.8	n.a.
Fever	6	4.4	5	3.0	n.a.
Bronchial hyperreactivity	4	2.9	6	3.6	n.a.
Otitis media acuta	3	2.2	5	3.0	n.a.
Influenza	2	1.5	10	6.1	n.a.
Viral respiratory tract infection	1	0.7	0	0	n.a.
Acute laryngitis/tracheitis	1	0.7	0	0	n.a.
Otitis media with effusion	0	0	1	0.6	n.a.
Sinusitis	0	0	1	0.6	n.a.
No diagnosis noted	1	0.7	5	3.0	n.a.
Total	**136**		**165**		

n.a.: not applicable, too few counts to perform statistical analysis

Point-of-care CRP was not measured in two children in the intervention group (1,4%), and in the control group point-of care CRP was measured 30 times (18,2%) in violation of protocol (figure 1). A per protocol analysis, excluding these 32 children, showed no significant difference in antibiotic prescription rates at the index consultation.

Due to missing consent of the parents for follow up, follow up data were only available for 180 children (58% of total, 81 children (57%) in the intervention group and 99 children (59%) in control group). Children in both groups had similar rates of re-consultations within the same episode of illness (33% vs. 34%; OR 0.95; 95%CI 0.46-1.99) and antibiotic prescriptions during these consultations (7% vs. 8%; OR 0.94; 95%CI 0.33-2.63). In the next three months, 16% of children in the CRP group consulted their GP for respiratory tract illness, compared to 29% in the control group (OR 0.61 95%CI 0.32-1.17) (Table 4). One child in the control group was admitted to hospital directly after inclusion.

CRP levels and antibiotic prescriptions

CRP levels ranged from <5 to 200mg/L, with 46% of children having a CRP level <10mg/L, 51% between 10 and 100mg/L, and 4% >100mg/L. Control children in whom CRP was measured

were not more seriously ill than other control children (mean illness severity 3.8 SD 1.8 in both groups), and their mean CRP level was not significantly different from the mean CRP level in children in the intervention group (mean 22.5 vs. 24.9; p=0.72).
Children were more likely to get an antibiotic prescription with increasing CRP level, ranging from 14% in children with a CRP level < 10 mg/L to more than 50% in children with a CRP level > 40mg/L (Figure 2).

Figure 1. trial profile

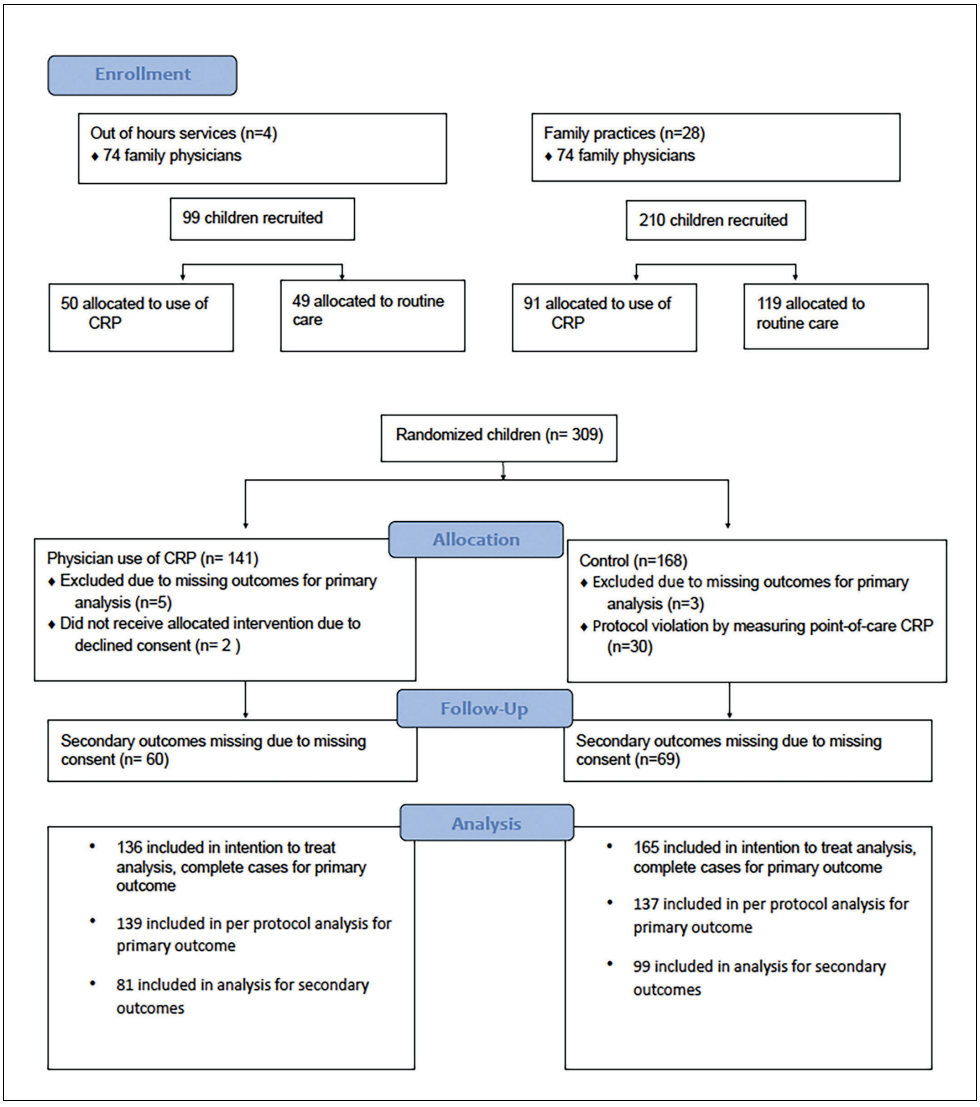
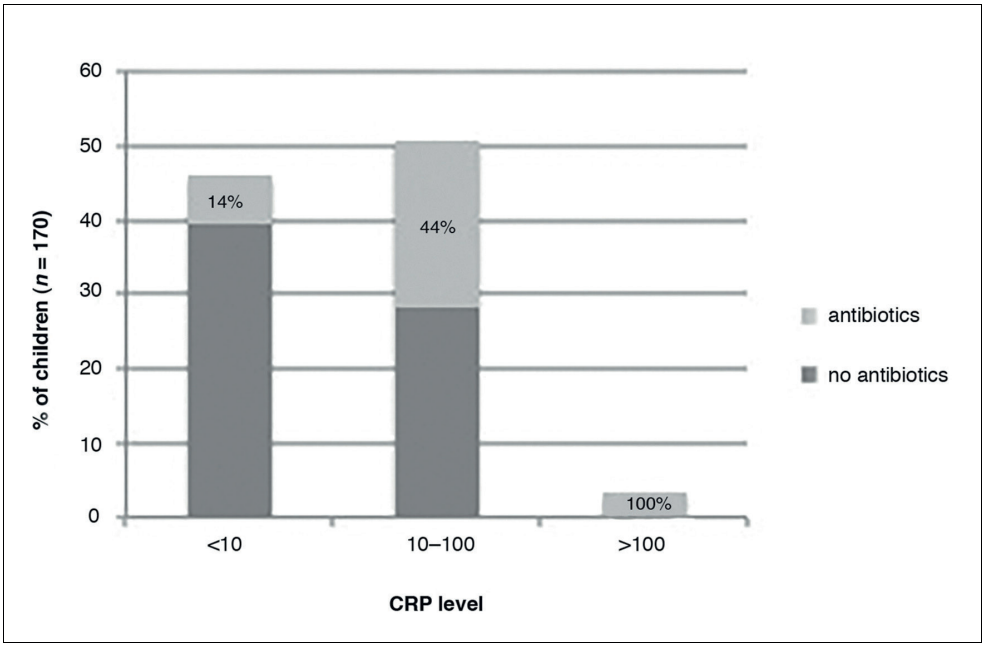


Figure 2. CRP levels and antibiotic prescriptions



DISCUSSION

In this open, pragmatic, randomized controlled trial in primary care, we did not find a significant effect on antibiotic prescribing for children with non-serious respiratory tract infection when GPs used point-of-care CRP: antibiotic prescribing was 30.9% in the CRP group versus 39.4% in the intervention group. Re-consultation and antibiotic prescriptions in the following three months also did not differ significantly.

Strengths and weaknesses

We used a pragmatic design, evaluating point-of-care CRP testing in daytime general practices and out-of-hours services, making the results generalizable to routine general practice. The cluster design in daytime general practices aimed to minimize learning effects and contamination. Nevertheless, there were protocol violations in our control group, potentially diluting the effect of CRP. A per protocol analysis however, equally did not find a significant effect.

Though we see a trend towards reduction in antibiotic prescriptions, we were unable to prove that this is statistically significant. This may in part be due to lack of power to detect this smaller than expected decrease. Antibiotic prescribing rates were lower than expected in both groups. Based on earlier studies in children with LRTI, we presumed an antibiotic prescription rate of

70% in the control group in our sample size calculation (1, 9). This lower prescription rate may have been caused by the recruited patient mix, in particular by the inclusion of children with an upper respiratory tract infection in whom antibiotics are known to be prescribed less frequently (10, 11, 32). Although we aimed to include children with LRTI and designed our inclusion criteria accordingly, there is a discrepancy between these criteria and the GP's reported diagnosis after complete assessment. Oftentimes a symptom based diagnosis, or an upper respiratory tract infection was reported. A diagnosis in general practice is a working diagnosis, not checked by a golden standard, and inter-rater agreement in ICPC coding in general practice is good at chapter level, but can differ on single code level (1). The open character of our study, with the GP unblinded to the CRP level before noting a final diagnosis, might have influenced diagnostic labelling. This hypothesis is supported by the fact that significantly more children in the intervention group were diagnosed with upper respiratory tract infection, in contrast with a significantly higher rate of bronchitis in the control group.

We did not reach our planned sample size (309 out of 354 children), despite a prolonged recruitment period and addition of the out-of-hours services for recruitment. This may have further affected the power of the study, and a larger study is necessary to decide whether point-of-care CRP can reduce antibiotic prescriptions. Although we aimed for a large reduction in the prescription of antibiotics based on results from trials in adults (33), we feel that if a future study could confirm our results, a decrease of 8.5% in antibiotic prescriptions in this group of primary care patients could be considered clinically relevant, as in other studies with the same aim in adults (34, 35).

Data for analysis of secondary outcomes were available for 58% of the children. Quite low follow-up rates were the result of a need for obligatory double informed consent in the Netherlands, signed by both parents, to collect follow-up data. This double consent proved difficult to obtain in general practice (36). We have no indication that loss to follow up was related to any other factors.

Comparison with previous studies

CRP levels in our study correspond with reported levels in adults (33) and children with respiratory infections (28, 37). Most children had low CRP levels, as is expected in a primary care setting, because most children suffer from non-serious illnesses. In a recent Norwegian study in children with fever and/or respiratory symptoms presenting to out-of-hours services, antibiotics were prescribed to 13% of children with CRP levels <20mg/L (38). In our study 14% of children with a CRP level <10mg/L were prescribed antibiotics. As in our study, a CRP level above 20 mg/L was found to be a strong predictor for the prescription of antibiotics.

Implications for clinical practice and further research

It is still uncertain whether point-of-care CRP can reduce antibiotic prescriptions for children with suspected non-serious LRTI. Future research should focus on this question.

Future research should also focus on the value that point-of-care CRP potentially has in more correctly identifying the children in primary care that suffer from pneumonia, as current evidence shows no definite cut-off levels that are useful to rule in the child in need of antibiotic treatment. This could lead to uncertainty in management of children with intermediate to higher CRP levels. More than half of children with a point-of-care CRP level >40mg/L in our study were prescribed antibiotics. CRP point-of-care testing was introduced in primary care for adults with LRTI, to support decisions on antibiotic prescribing (23). This may have led GPs to consider elevated CRP levels as a proxy for bacterial infection automatically warranting antibiotics. However, CRP levels do not allow differentiation between bacterial or viral origin of infection, but are a proxy for the disease severity (17-19). Therefore, an elevated CRP level in children is a red flag for potential serious infection. This may require treatment with antibiotics, but should especially prompt the GP to ensure proper instruction of parents and careful safety netting. Efforts should be made to educate GPs on the current evidence on the value of point-of-care CRP for children. Further research is necessary to provide them with threshold-specific recommendations.

In our study, children with low CRP levels were prescribed antibiotics, although children who were judged as severely ill or highly suspected of having pneumonia were excluded from our study, and despite evidence that CRP levels below 5mg/L can rule out serious infections requiring hospitalization in children safely (28). Knowledge on the GPs' reasoning behind these prescriptions, including possible non-medical reasons, might provide further insights to better target interventions for antibiotic stewardship.

CONCLUSION

It is still uncertain whether point-of-care CRP measurement in children with non-serious respiratory tract infection presenting to general practice can reduce the prescription of antibiotics. Until further research provides more evidence, point-of-care CRP measurement in children with non-serious respiratory tract infection is not recommended.

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CHAPTER 6

Wet- en regelgeving vormt bedreiging voor niet-farmacologisch wetenschappelijk onderzoek bij kinderen

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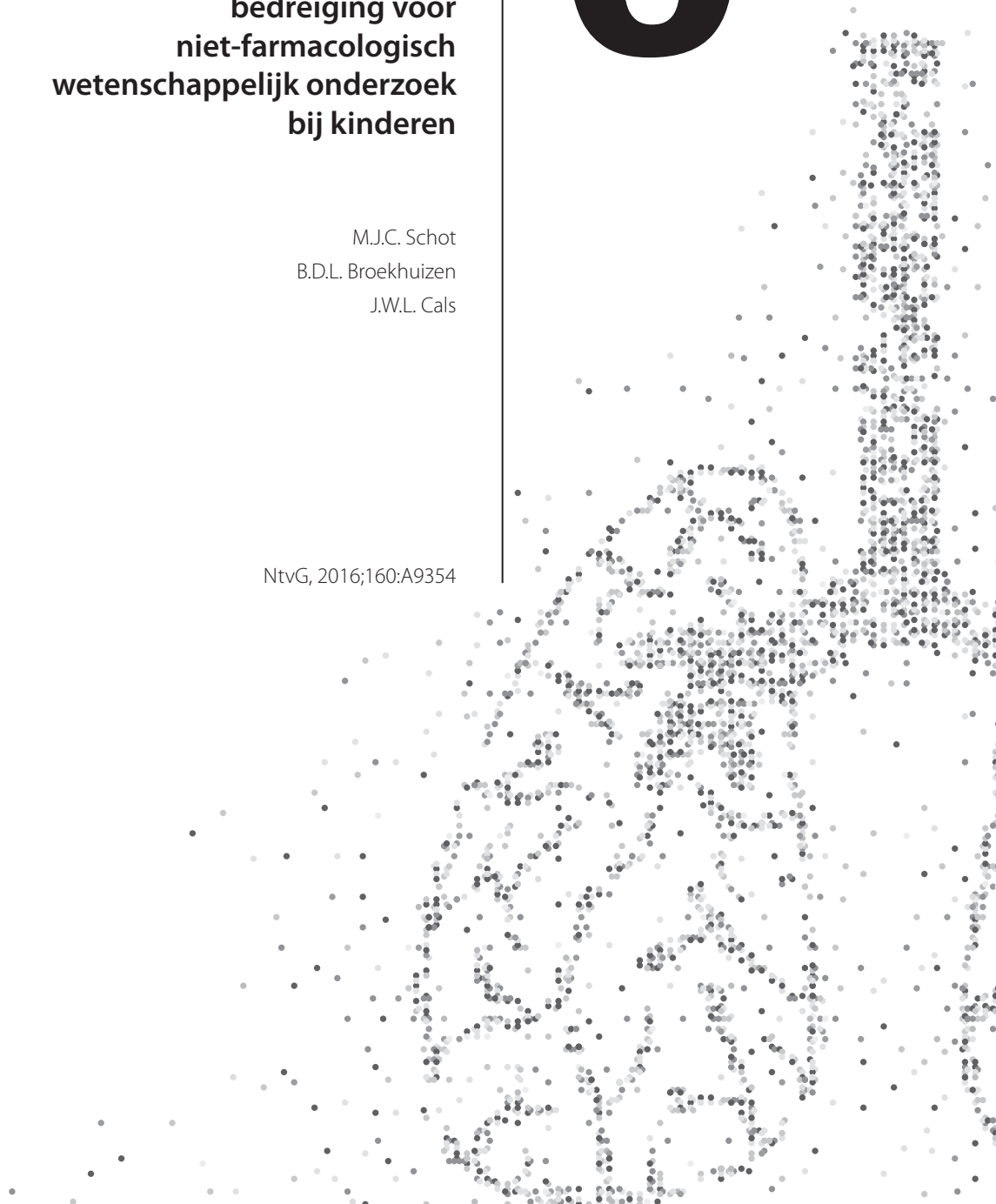

NEDERLANDSE SAMENVATTING

Veel niet-farmacologische interventies zijn wetenschappelijk onderzocht bij volwassenen, maar bewijs om deze interventies toe te passen bij kinderen ontbreekt. Het is belangrijk dat de bewijskracht voor niet-farmacologische interventies bij kinderen toeneemt maar wet- en regelgeving maakt dit type onderzoek momenteel moeilijk uitvoerbaar. Wij beschrijven huidige wetten en regels die van toepassing zijn op medisch wetenschappelijk onderzoek bij kinderen, bediscussiëren de obstakels en suggereren oplossingen.

ENGLISH SUMMARY

Many non-pharmacological interventions have only been tested in adults, and evidence on using these in children is lacking. To enhance child healthcare, research is required into these interventions in children. However, current rules and regulations make it difficult to conduct research into these low-risk, minimal-burden interventions. We describe the current rules and regulations on conducting research in children in the Netherlands and discuss the possibilities for adapting certain rules in accordance with the type of research that is performed.

Een kind is geen kleine volwassene, maar veel wetenschappelijk bewijs voor de dagelijkse medische praktijk is gebaseerd op onderzoek met volwassenen, dat vervolgens wordt toegepast op kinderen. Een recent artikel in dit tijdschrift beschreef het belang van meer geneesmiddelenonderzoek specifiek bij ernstig zieke kinderen (1), en ook de commissie Doek benadrukte in 2009 de noodzaak van meer interventieonderzoek bij kinderen (2). Wij vinden het belangrijk dat er ook meer onderzoek plaatsvindt naar niet-farmacologische interventies die al worden toegepast op volwassenen, terwijl er voor gebruik bij kinderen nog onvoldoende wetenschappelijke onderbouwing is. Dit type onderzoek heeft hooguit een verwaarloosbaar risico en minimale belasting voor de deelnemende kinderen, maar bij de uitvoering gelden dezelfde wetten en regels als bij experimenteel geneesmiddelonderzoek. Wij illustreren aan de hand van een voorbeeld studie waarom dit de uitvoering van onderzoek naar niet-farmacologische interventies momenteel moeilijk maakt. Aan de hand van voorbeelden uit deze studie suggereren wij oplossingen en pleiten we voor meer maatwerk in de toepassing van wetten en regels bij wetenschappelijk onderzoek bij kinderen.

Voorbeeldstudie: een vingerprik bij kinderen

Het is bewezen dat het gebruik van de C-reactief proteïne (CRP) sneltest de huisarts helpt om gerichter antibiotica voor te schrijven bij volwassenen met hoestklachten. Inmiddels is de CRP sneltest onderdeel geworden van de reguliere huisartsenzorg en adviseert de NHG Standaard Acuut Hoesten de test bij diagnostische onzekerheid bij een matig zieke volwassene met acute hoestklachten (3). De helft van de Nederlandse huisartsen heeft een CRP sneltest in de praktijk (4). Voor de test wordt een druppel bloed afgenomen middels een vingerprik, en de huisarts gebruikt de uitslag die binnen enkele minuten beschikbaar is direct bij zijn beleid.

Ook bij kinderen met acute hoestklachten kan er diagnostische onzekerheid bestaan. Hoewel de richtlijn stelt dat de waarde van een CRP sneltest bij kinderen onvoldoende is onderzocht (3), verrichten huisartsen soms toch een CRP sneltest bij kinderen, ook omdat deze diagnostiek nu eenmaal beschikbaar is. In 2013 startten wij een gerandomiseerde interventiestudie om de waarde van de CRP sneltest te beoordelen bij deze 'nieuwe' doelgroep (Nederlands trialregister code 4399). Het is een onderzoek naar een niet-farmacologische interventie en de vereiste vingerprik is minimaal belastend en zonder risico's voor het deelnemende kind. Naast de CRP-meting verzamelen we follow-up gegevens en houden ouders een klachtendagboek bij. Wij zullen in enkele voorbeelden refereren naar dit onderzoek als voorbeeldstudie.

Obstakel door Nederlandse wetgeving

Bescherming van minderjarigen is het uitgangspunt bij het opstellen van veel wetten en regels. Zo moet een arts altijd toestemming vragen voorafgaand aan een behandeling of interventie bij een minderjarige. De procedure hiervoor bij een reguliere medische behandeling van een kind tot 12 jaar staat beschreven in de Wet Geneeskundige Behandelingsovereenkomst (WGBO). Volgens de

WGBO moet een arts voorafgaand aan een diagnostische handeling of behandeling toestemming vragen aan alle gezaghebbenden, in de meeste gevallen beide ouders. In de praktijk is dit onwerkbaar en zodoende geldt dat als een van beide gezagdragende ouders op het spreekuur komt, de arts ervan uit mag gaan dat deze mede namens de andere gezagdragende ouder spreekt. Alleen als er aanwijzingen zijn dat dit niet zo is, moet de arts deze ouder ook expliciet om toestemming vragen (5). Bijvoorbeeld: een moeder komt op het spreekuur met haar kind van 8 jaar omdat hij vermoeid is. De huisarts bespreekt dat hij bloedonderzoek wil doen en moeder stemt hiermee in. De arts mag er in dit geval vanuit gaan dat de vader van het kind ook instemt met het gevraagde onderzoek.

Medisch wetenschappelijk onderzoek met kinderen mag in Nederland alleen worden uitgevoerd als er aan bepaalde eisen is voldaan. Aan onderzoek dat henzelf niet te goede komt (zogenaamd niet-therapeutisch onderzoek), mogen alleen minderjarigen deelnemen als het onderzoek enkel in deze groep kan worden uitgevoerd (groepsgebondenheid), de risico's hooguit verwaarloosbaar zijn en de bezwaren niet meer dan minimaal. Deze eisen staan beschreven in de Wet Medisch Wetenschappelijk Onderzoek (WMO) (6). De METC of CCMO bepaalt of een onderzoek mag worden uitgevoerd. Voor daadwerkelijke deelname aan medisch wetenschappelijk onderzoek door een kind jonger dan 12 jaar zijn de regels voor toestemming in principe hetzelfde als voor een reguliere behandeling: beide ouders moeten toestemmen. Echter, bij medisch wetenschappelijk onderzoek moet deze toestemming schriftelijk worden vastgelegd en mag een arts er bij toestemming van een ouder níet vanuit gaan dat de andere ouder ook toestemming geeft. Deze procedure geldt op dit moment voor elk type medisch wetenschappelijk onderzoek, ongeacht de belasting en de risico's voor het kind.

De verplichte schriftelijke toestemming van beide ouders zorgt bij de voorbeeldstudie voor problemen. Voorafgaand aan de vingerprik moeten namelijk beide ouders schriftelijk toestemming geven. Dit terwijl vrijwel alle kinderen maar met één ouder op het spreekuur komen en de CRP sneltest wel tijdens het spreekuur uitgevoerd moet worden, zodat de huisarts de uitslag direct kan gebruiken voor zijn beleid. Het is dus niet haalbaar om te wachten op de schriftelijke toestemming van de afwezige ouder. Deze procedure lijkt disproportioneel voor dit type onderzoek, want een vingerprik is een minimaal invasief onderzoek met verwaarloosbare risico's. Het bepalen van het CRP om de ernst van infectie in te schatten brengt ook geen andere risico's met zich mee, zoals dat bijvoorbeeld wel het geval kan zijn wanneer het bloed wordt opgeslagen of gebruikt voor genetisch onderzoek.

Disproportionele eisen vanuit Europese regelgeving

Naast Nederlandse wetgeving is er ook Europese regelgeving, zoals de richtlijn Good Clinical Practice (GCP) (7). Volgens de Nederlandse wet hoeft alleen geneesmiddelenonderzoek te voldoen aan

de GCP richtlijn. Desondanks leggen Nederlandse onderzoeksinstituten deze richtlijn als bindend op bij elk wetenschappelijk onderzoek, zonder onderscheid op basis van bijvoorbeeld belasting of risico voor de proefpersonen. De opgelegde regels leiden vaak tot onnodige bureaucratische procedures die niet passen binnen een onderzoek zonder risico's en met minimale belasting.

GCP stelt eisen aan de schriftelijke informatie voor proefpersonen waardoor de informatiebrief in de voorbeeldstudie 4 A4-tjes beslaat. Dit is te veel om in korte tijd te lezen en begrijpen. Wij denken dat het goed mogelijk is om alle belangrijke punten van ons onderzoek op een bladzijde samen te vatten zonder onvolledig te zijn. Ook zijn er eisen voor het toestemmingsformulier. Hierop moet de huisarts de datum, zijn naam en handtekening zetten. GCP vereist dat de huisarts zijn naam met de hand schrijft, en niet met de in de praktijk veel gebruikte stempel. Ook beide ouders moeten elk zelf hun naam schrijven. Strikte voorschriften zoals deze leiden ons inziens tot frustratie bij de includerende arts, de onderzoeker en de ouders, hetgeen inclusie belemmert en vertekening bevordert, en dus niet zorgt voor een verbetering van dit type onderzoek.

De vele vereisten leiden ertoe dat onderzoekers in de toekomst geen onderzoek met kinderen meer willen doen of kiezen voor zogenaamd niet-WMO plichtig onderzoek, waarbij reguliere zorg zonder interventie wordt onderzocht. Hierdoor worden innovatieve interventies bij kinderen onvoldoende geëvalueerd, en neemt de bewijskracht voor toepassing bij kinderen niet toe. Huisartsen zijn al steeds minder bereid om deel te nemen aan wetenschappelijk onderzoek, omdat het onderzoek niet goed aansluit bij de dagelijkse praktijk (8). Een complexe toestemmingsprocedure en omslachtige administratie leidt tot een verdere afname van de bereidheid tot deelname aan wetenschappelijk onderzoek door huisartsen specifiek, maar ook door andere zorgprofessionals die met kinderen werken.

WMO en GCP op maat!?

Wij denken dat de WMO aangepast moet worden. In veel landen voldoet toestemming van één ouder, gebaseerd op mondiale afspraken zoals de verklaring van Helsinki, die spreekt over toestemming van één ouder (9). Wij denken dat bij een onderzoek dat minimaal belastend is en hooguit verwaarloosbare risico's met zich meebrengt, zowel de (huis)arts als de ouder de consequenties van deelname aan het onderzoek goed kunnen overzien. Dit geldt zeker voor interventies die soms al worden toegepast in de praktijk, maar nog niet voldoende wetenschappelijk zijn onderbouwd, zoals in de voorbeeldstudie. Voor dit type onderzoek zou een lokale METC, zo nodig met ondersteuning van het landelijke orgaan de CCMO, moeten mogen beoordelen of het proportioneel en haalbaar is dat beide ouders toestemming geven voor deelname, of dat toestemming van één ouder voldoende is. Bij de inschatting van de risico's en de belasting van het onderzoek, kunnen dezelfde beginselen gelden als bij de WGBO. Aanpassen van wetgeving is echter een langdurig proces en behelst politieke beslissingen, waar wetenschappers maar tot op

zekere hoogte invloed op hebben. De dagelijkse uitvoering van de GCP-richtlijn valt echter wél binnen de directe invloedsfeer van wetenschappers.

Farmacologische studies vormen een fractie van het noodzakelijke onderzoek naar bruikbare interventies om de zorg voor kinderen te optimaliseren. Juist bij onderzoek naar niet-farmacologische en hooguit minimaal invasieve interventies bij kinderen dient het toepassen van de strikte GCP regels te worden (her)overwogen. Wettelijk hoeft alleen geneesmiddelenonderzoek aan alle eisen van GCP te voldoen. Het is belangrijk dat METCs, onderzoekers en zo nodig ook bestuurders van onderzoeksinstellingen afstemmen aan welke regels van GCP moet worden voldaan en welke (administratieve) regels, gezien bijvoorbeeld de minimale risico's van het onderzoek, niet hoeven te worden nageleefd. Dit maakt maatwerk mogelijk met een optimale balans tussen zinvolle procedures uit wet- en regelgeving en praktische uitvoerbaarheid in de praktijk. Dit alles zonder de bescherming van de proefpersoon uit het oog te verliezen.

Het risico van steeds uitvoerigere wet- en regelgeving rondom wetenschappelijk onderzoek bij kinderen is dat het kind als proefpersoon in Nederland zó goed beschermd wordt, dat het onderzoek niet uitvoerbaar is, waarna het kind vervolgens in de reguliere zorg wordt blootgesteld aan een interventie zonder wetenschappelijk bewijs. Of zoals een recent commentaar in The Lancet bij een rapport over kinderen en klinisch onderzoek stelt: "The time has come to protect children and young people *through* research not *from* research" (10).

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CHAPTER 7

General discussion

The general discussion will be used to sum up the main findings of this thesis and to further discuss a number of key issues. The previous chapters contain data from a cohort of 149 children with respiratory tract infection (RTI), a systematic review of 17 studies and a cluster randomized trial on the effect of point-of-care C-reactive protein (CRP) testing in 309 children with suspected lower respiratory tract infection (LRTI) included by 148 participating general practitioners (GPs). Furthermore, qualitative data on the use of point-of-care CRP in children were collected in interviews with GPs. The first part of this discussion contains the main findings and the answers to the research questions. Thereafter, we will further discuss the value of point-of-care CRP testing in children with suspected LRTI in general practice, and compare our results with other currently available evidence. Specifically, we will discuss why point-of-care CRP testing in children does not seem to cause a relevant reduction of antibiotic prescriptions for children. Third, we will elaborate on some of the methodological considerations. We will focus on difficulties in recruitment of children for trials in general practice and argue if cluster randomization was appropriate in our trial. Lastly, we will discuss what can be the aim of future research and how these studies could be designed.

MAIN FINDINGS OF THIS THESIS

1. What is the impact of RTI on the general wellbeing of children and their parents?
RTI causes symptoms like cough and nasal congestion, but also affect a child's general wellbeing. After consultation, children will experience symptoms as disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities on average for another 4 to 5 days. RTI also has impact on the child's family as nearly half of the children stay home from childcare or school during the first week after consultation, but also nearly half of the parents reported absence from work, on average for eight hours. Because RTI is so common the overall burden of RTI for children, families and society is high.

2. What is the diagnostic value of signs, symptoms and additional diagnostic tests for pneumonia in ambulant children with signs of a respiratory tract infection?
Children with symptoms of RTI frequently present to a GP. It is the GP's task to determine whether the child is suffering from an RTI that is merely self-limiting, or whether there is a suspicion of a more serious infection, such as pneumonia, or if there are risk factors for developing such an infection. A systematic review of the literature revealed that very few diagnostic studies are conducted in settings with low prevalence of pneumonia and no single item from history taking, physical examination or additional laboratory testing appears to be sufficient to diagnose pneumonia in ambulant children.

In our review four studies were selected that reported on the diagnostic value of laboratory

tests in diagnosing pneumonia, three with the aim to develop a clinical prediction model to identify children with a serious bacterial illness, including pneumonia. All four studies showed significantly higher values of CRP and mean white blood cell count in the presence of pneumonia. The diagnostic models, initially based on signs and symptoms, improved when CRP was added. None of the selected studies provided data on specific cut-off points for the various laboratory tests, or the corresponding univariate values for positive predictive value and negative predictive value.

3. Do GPs' perceptions of the use of point-of-care CRP testing in the diagnostic evaluation of children with LRTI differ from their perceptions of the use of this test in adults, and if so in what respect?

We found that GPs' perceptions of the addition of point-of-care CRP testing in children with suspected LRTI differ from their perceptions of this additional test in adults. We identified five themes that explained this difference. GPs felt that a child was a vulnerable patient, with a different clinical presentation than an adult. Furthermore, they felt that there was not yet enough evidence on the use of point-of-care CRP in children. In particular they mentioned that the lack of clear cut-off values for the need to prescribe antibiotics or for the treshold to safely abstain were lacking. A fourth difference between children and adults was seen in the impact of the test procedure. GPs perceived that while they could explain the necessity of a finger prick to an adult patient and considered it of low impact, this was different in children. They feared adverse reaction and the potential risk of avoiding to visit the GP in the future. Lastely GPs mentioned that point-of-care CRP was not only used as a diagnostic tool in adults, but also as a way of communicating a non-prescribing message. They felt that this was not a valid reason to use point-of-care CRP in children. For this, specifically two reasons were mentioned by GPs: they felt that the impact of the procedure did not justify this indication, and they felt less pressured by parents to prescribe antibiotics in the first place, making communication about non-prescription less difficult in children compared to adults.

4. Does introduction of point-of-care CRP to the diagnosis of LRTI in children in primary care reduce prescription of antibiotics?

In this thesis we evaluated the effect of point-of-care CRP measurement in children with non-serious respiratory tract infection presenting to general practice on the prescription of antibiotics. Antibiotic prescribing rates did not significantly decrease when the GP used point-of-care CRP. Antibiotic prescribing rates in the trial were lower than expected, with 30.9% and 39.4% of children receiving antibiotics in the intervention and the control group respectively. 46% Of children had point-of-care CRP levels below 10mg/L.

ANTIBIOTIC PRESCRIBING IN CHILDREN WITH RTI; IS THERE A ROLE FOR ADDITIONAL DIAGNOSTIC TESTING?

Antibiotics are frequently prescribed to children in primary care. In total, nearly one in six children <12 years of age received at least one course of oral antibiotics in the Netherlands. Antibiotics were prescribed in one of four consultations at the out-of-hours service for children consulting with fever (1,2). The youngest children most frequently consult a GP, and are also prescribed antibiotics most frequently . In children aged 0-2 years, acute upper respiratory tract infection (URTI) is the second most frequent indication to prescribe antibiotics, for 14% of the episodes, an antibiotic is prescribed (3).

In contrast, clinical guidelines advise to prescribe antibiotics only in case of LRTI with an increased risk of complications or with a prolonged course . A study examining guideline compliance found that prescription rates would be around 20% if GPs fully complied to the guidelines (4), and 48-63% of antibiotic prescriptions for RTI in children were regarded to be non-compliant with guidelines (4,5). More antibiotics are prescribed at an out-of-hours service compared to daytime general practice, but the percentage that is non-compliant with guidelines is not higher (6). Though there may be relevant reasons to deviate from guidelines, it is also important to note that severe bacterial infections are rare, and the number of serious infections is declining partly due to increased vaccination. The true prevalence of pneumonia is unknown, as there are no studies that validate every pneumonia diagnosis made by GPs. The reported prevalence of serious illness in children in primary care varies from 0.3% to 12.5% (7,8). These data show that there is room for reducing the amount of antibiotics prescribed to children. One of the main reasons GPs prescribe antibiotics to children is diagnostic uncertainty. Addressing this issue may reduce inappropriate prescribing of antibiotics in children with RTI.

Diagnostic uncertainty could be decreased by additional (laboratory) testing, provided the tests used are valid and have added diagnostic value. Point-of-care tests can directly support clinical decision making because they are performed during or directly after consultation, with results available at the time of clinical decision making (9). Point-of-care tests have the potential of saving time while optimizing management, reducing referrals to hospital and reducing health care costs. CRP was first identified as a diagnostic marker in secondary care. With availability as a point-of-care test, it had potential to be used as a diagnostic marker in primary care. As such, it was evaluated first for diagnosing pneumonia in adults in primary care.

VALUE OF POINT-OF-CARE CRP TESTING IN ADULTS WITH RESPIRATORY TRACT INFECTION IN PRIMARY CARE

C-reactive protein as a single test is not adequate in either ruling-out or ruling-in pneumonia in adults in primary care (10). However, in daily practice, the GP combines signs, symptoms and additional tests such as CRP to set a probable diagnosis. The added value of measuring CRP in the diagnostic

process of pneumonia has been shown in adults, most recently in a large meta-analysis of individual patient data (11). In diagnosing pneumonia, the pooled estimate of the improvement in area under the curve was 0.075 (95% CI 0.044–0.107) when adding CRP. More importantly, CRP improved risk classification. Three diagnostic risk groups for pneumonia were defined: low risk (predicted probability < 2.5%), intermediate risk (predicted probability 2.5%–20%) and high risk of pneumonia (predicted probability > 20%). When combining signs and symptoms with CRP measurement, the discrimination between patients with and without pneumonia improved. The addition of CRP improved diagnostic risk classification by increasing the proportion of patients without pneumonia correctly identified as low-risk patients (true negative) by 8% (to 36% in total). It also increased the proportion of patients with pneumonia correctly identified as high risk (true positives), from 63% to 70%. The proportion of false negative results declined from 2% to 1% and the proportion of false positive results decreased from 58% to 49% when CRP was added. 51% Of patients were classified as having an intermediate risk of pneumonia (2.5%-20%) after addition of CRP.

Although addition of CRP to the clinical evaluation by the GP still leaves a substantial proportion of the patients in the intermediate risk category for pneumonia, CRP was found to reduce antibiotic prescription in adults. In 2014, Aabenhus et al. systematically reviewed evidence specifically on its use in primary care to guide antibiotic prescription to adult patients with respiratory tract infections (12). They conclude from combining six trials that using point-of-care CRP can reduce antibiotic use without negative impact on recovery from and duration of illness.

Qualitative studies on the use of point-of-care CRP for adults with respiratory tract infections show that clinicians generally have a positive perception of the use of the test. GPs reported that point-of-care CRP increased their diagnostic certainty and could inform prescribing decisions which they felt could lead to less antibiotic prescribing. GPs expressed that it helped in educating and communicating with patients about antibiotics (13–16). Concerns on the introduction of point-of-care CRP were also comparable across different studies and included costs, test accuracy and detraction from clinical reasoning (13,14,16). Interpretation of ambiguous tests results was also specifically mentioned (14,15).

The evidence on the diagnostic value of CRP and its' effect on antibiotic prescribing in adults resulted in its incorporation in clinical guidelines internationally (17,18). The value of CRP in children is less studied, but has been subject of interest especially the past years.

VALUE OF POINT-OF-CARE CRP TESTING IN CHILDREN WITH RESPIRATORY TRACT INFECTION IN PRIMARY CARE

In children, research on the diagnostic value of CRP in general practice has focused mainly on diagnosing serious illness, including pneumonia. A true diagnostic study to assess the value of CRP in diagnosing pneumonia in children in primary care has not been performed.

A cohort study conducted at Dutch out-of-hours services evaluated whether CRP had added value

in diagnosing serious illness in 440 febrile children (8). Using a broad definition of serious illness, to be diagnosed by the treating GP, the prevalence of serious illness in this study was 12.5%. At a cut-off level of <20mg/L, researchers found no difference in the probability of having no serious illness (pre- and post-test probability 87.5%). Using a cut-off value of >80mg/L however, CRP significantly increased the probability of having serious illness (12.5% vs 21.2%).
A cluster randomized trial conducted in Belgium evaluated the improvement of risk classification by adding point-of-care CRP to a validated clinical prediction rule (19). The primary outcome measure was hospital admission within 5 days after initial presentation with a serious illness. The clinical prediction rule scored children on breathlessness, body temperature of at least 40 °C, diarrhea in children 12–30 months of age, and clinician's concern (20). This prediction rule identified 20% of the included children to be at risk for serious infection. The addition of CRP, with a threshold of 5mg/L, increased specificity from 80% to 89% and increased the positive predictive value from 1.4% to 2.4%, while the sensitivity remained at 100%. So, the combination of a positive clinical prediction rule with a low CRP ruled out serious infection requiring hospitalization. However, the chosen outcome measure of hospitalization leaves an important clinical question unanswered: how should children that do not require hospitalization be managed in primary care? Is it also safe to withhold antibiotics in children in whom there is no need for hospitalization? The effect of point-of-care CRP testing on antibiotic prescribing for children with acute infections was studied in the same cluster randomized trial by Lemiengre et al. (21). In this analysis, children identified to be at high risk for serious infection by the clinical decision rule were excluded, as authors stated that antibiotic prescribing should not be restricted in those cases. There were 1027 children included in the analysis. Participating GPs were not given guidance on how to interpret CRP values, or instructed when to withhold or prescribe antibiotics. Overall, in comparison to usual care, point-of-care CRP measurement did not reduce the prescription of antibiotics (adjusted odd ratio 1.01 (95% confidence interval 0.57-1.79)). Interestingly, secondary analysis showed that when CRP was measured, a CRP level <5mg/L decreased the amount of antibiotics prescribed to children (23). This finding suggests that GPs do take the level of CRP into account when making a prescribing decision.

Only one small mixed method study also qualitatively evaluated the use of point-of-care CRP for children in primary care (22). The five participating GPs in this study had little or no experience with this diagnostic instrument. Their views on the addition of point-of-care CRP to their diagnostic process were inconsistent, with a need for more evidence and clear guidance regarding the diagnostic value of point-of-care CRP in children as identified themes.

No overall reduction in antibiotic prescriptions when measuring CRP in children: why?
Similar to the study mentioned above, we also found no significant reduction in the prescription of antibiotics when GPs measured CRP in children with non-serious respiratory tract infections

compared to usual care. So, a successfully implemented CRP based strategy to reduce antibiotics in adults does not seem to work in children. There are several possible explanations for this result. First, the true diagnostic value of CRP in children in primary care for diagnosing pneumonia has never been studied. A diagnostic trial, with all children suspected of pneumonia being evaluated with the reference test (CRP) and the gold standard (chest X-ray) has many ethical and practical obstacles. In the absence of such a trial, guidance on cut-off values for CRP on when to prescribe or withhold antibiotics are not available for children. Specifically, the absence of a cut-off value below which it was safe to withhold antibiotics, was mentioned by some GPs as a barrier to use CRP in children in our qualitative study in chapter 4.

Moreover, even if evidence-based cut-off levels would be available, it is uncertain whether CRP as a diagnostic marker in children in primary care would have effect on antibiotic prescriptions. In adults, GPs seem to have accepted that a small percentage of patients with a CRP below 20mg/L will have pneumonia (approximately 1%), and the advice in the guideline not to prescribe antibiotics to patients with a CRP below 20mg/L is quite strictly adhered to in daily practice. However, the established cut-off values in adults place about half of the adult patients in an intermediate risk group, and this will likely be similar for children. As children are generally perceived as a more vulnerable group of patients, GPs seem less willing to accept the potential of missing a serious illness in children. It is therefore likely that they weigh evidence differently, and need more certainty. The fact that Lemiengre et al. found that GPs do adjust their prescription behavior, as CRP levels <5mg/L decreased the number of antibiotics prescribed to children in their trial, shows that GPs may be susceptible to lower their prescribing rates when CRP is not elevated at all (23).

A second explanation for the fact that no reduction in antibiotic prescriptions was found is the fact that point-of-care CRP test results are used to legitimate a nonprescription message. Qualitative studies have shown that GPs mention this as an advantage of point-of-care CRP measurement in adults. A low CRP level is used as extra support to convince the patient that antibiotics are not necessary (15). Contrastingly, in our qualitative study, we found that GPs felt that they could not use the test for this purpose in children.

Should we implement the use of CRP in children? Is there an alternative?

Given the current evidence, the routine use of point-of-care CRP in children should not be recommended. However, as point-of-care CRP has been implemented and is widely available in primary care in the Netherlands, efforts should be made to further evaluate the use of CRP testing. As Lemiengre et al. found restricted antibiotic prescribing by GPs when CRP was below 5mg/L (23), it does seem that GPs are willing to incorporate a CRP value in their decisions. Possibly, even better education on the available evidence of CRP might increase its value for GPs. Furthermore, identifying the group of children in whom antibiotics can be safely withheld seems most relevant. With the data collected so far, it might already be possible to identify clearer cut-off values below

which antibiotics can be safely withheld. This should also be the focus of future research.
As said, more diagnostic certainty is important in reducing inappropriate antibiotic prescribing. Currently, the only other diagnostic marker available as point-of-care test is procalcitonin. The diagnostic value of this biomarker has not been evaluated in children in primary care, but showed to have no diagnostic value in adults (24). Developing technology might provide us with novel diagnostic markers. As identified in our systematic review in chapter 3, ultrasound diagnosis may be promising for the future. Though possibly not suitable for regular use in primary care, it also holds potential as gold standard in future clinical trials, with high diagnostic accuracy without the disadvantage of children being exposed to radiation.

METHODOLOGICAL CONSIDERATIONS

Patient recruitment for prospective studies in general practice
Evidence from trials conducted in secondary care cannot automatically be transferred to primary care because of the differences between patients and disease presentation in primary and secondary care, including differences in prevalence of disease, severity of symptoms and prognosis. Fortunately, the body of evidence from trials conducted in primary care is growing rapidly. However, performing prospective clinical trials in primary care is challenging. One of the main challenges lies in the recruitment of sufficient patients to reach the predetermined sample size.
The recruitment of patients regularly takes more time that researchers anticipated. When trial recruitment starts, the number of eligible patients often drops far below the anticipated number of patients, only to go back up directly after recruitment ends. This phenomenon, described by an American clinical pharmacologist Louis Lasagna, has been named Lasagna's law. Lasagna's law especially applies to trials where patients who present to the GP with symptoms for the first time have to be included, so called 'incident cases' (25). This requires more effort from a GP: awareness of inclusion criteria, identification of eligible patients, and informing and inviting patients to participate. Depending on the inclusion procedure for the trial, this may affect the consultation to a greater or lesser extent. Barriers and strategies to minimize difficulties with patient recruitment have been identified. Recommendations include keeping in- and exclusion criteria simple, adapting study procedures to practices' wishes, keeping the burden for the GP and practice to a bare minimum, appointing research personnel to inform patients eligible for inclusion, and financial rewards (25–27). Though some of these recommendations are straightforward, one of the key challenges is that in general practice research support is not routinely available. Designing a study that causes the least possible deviation from the tight schedule in practice seems key to successful recruitment. Herein lies a task for researchers. However, GPs must also realize the importance of research in primary care to enhance our daily practice, and take on their important role in including patients for studies and collecting data.

Recruitment of children in prospective studies in general practice

For many non-pharmacological interventions, evidence for use specifically in children is lacking. Also for the use of point-of-care CRP to reduce antibiotic prescriptions, quite extensive research had been conducted in adults but evidence on its' use in children was lacking. In hindsight, the conclusion that the effect of measuring CRP is not the same for children and adults, underlines the importance of conducting the trial in children. However, conducting a trial with children adds to the before mentioned challenges in recruitment of patients. In chapter 6 of this thesis, we described some of the encountered issues and possible consequences.

The main obstacle we encountered was the obligatory double informed consent signed by both parents before a child could be included in the study. This need for double informed consent is laid down by law in the Netherlands (28). In an international perspective this is exceptional, as many other countries require consent of only one parent (29). As we discussed in detail in chapter 6 of this thesis, we argue that this law should be adjusted, as it negatively impacts recruitment, while it lacks a valid legitimation in low risk studies. We found that as we expanded our trial to the out-of-hours services, more often both parents were present during the consultation and the informed consent procedure was less of a barrier for inclusion. Moreover, as more children presented to the out-of-hours service as compared to single practices, it was feasible to have a research assistant on site. This meant that the burden on GPs was lower, and recruitment rates were higher.

Choosing cluster randomization

Cluster randomization is chosen when an intervention is not targeted at individuals, but on a higher level. For example, when an intervention is targeted at a GP with the intention to change patient outcomes. All patients treated by the same GP are then considered one cluster. Often, patients in such a cluster are more similar to each other with respect to confounders or outcomes, than to patients from a different cluster. Another reason to choose cluster randomization is when there is high risk of contamination between the study groups. For our trial, we chose cluster randomization at practice level as we presumed that individual randomization might introduce bias. Using point-of-care CRP might induce a learning effect where GPs would learn to relate CRP values to their clinical evaluation. In that way, they could use their knowledge of CRP values even in children that were randomized to the control group.

A consequence of cluster randomization is that data from individual patients are not independent from each another as they are influenced by a common factor. Cluster randomization leads to some loss of power due to supposed correlation of the cluster members, and this should be taken into account when designing the study and performing the sample size calculations (30,31). The needed sample size increases, taking into account an intra-cluster coefficient and the size of the clusters in a trial.

Another challenge with cluster randomization is the possible introduction of selection bias. Especially when there is no blinding of the GP who recruits and includes the patients, but also of

the patients prior to consent. GPs, aware of their allocation, might not enroll patients with certain characteristics, and cause differences in the study groups. Patients, aware of allocation, may base their consent on this information. These differences may affect study results (32–34). Different strategies have been proposed to minimize selection bias, including identifying and consenting of participants before randomization or blinded recruitment by a third party. This however is very difficult to incorporate in a busy daily care routine and although we asked GPs to obtain consent before telling patients in which trial arm their practice was, it is uncertain GPs always complied to that instruction. When reviewing the baseline characteristics of the children in our trial, we only found an imbalance in social economic status, which we corrected for in the analysis of the trial. However, there is a possibility that there were also other unmeasured characteristics that differed.
In hindsight, it is debatable that our trial could have been individually randomized. We review our main reason for cluster randomization: the possible learning effect during the course of the trial.
It may well be possible that this learning effect has already taken place and is no longer correctable through cluster randomization. As many GPs in the Netherlands have ready access to point-of-care CRP measurement, we found that GPs in the control group were also familiar with measuring CRP, and even did so in violation of protocol during the trial. On the other hand, we found that GPs in the intervention group, also familiar with point-of-care CRP, were reluctant to measure it when there was little doubt in their diagnostic process. This was elicited in the qualitative study in chapter 6.

Challenges that come with conducting a trial with children in primary care should not be underestimated. Considering the difficulties in recruiting patients, and especially children for prospective trials in primary care, efforts should be made to avoid the need for cluster randomization. In our opinion, a future (diagnostic) trial does not necessarily need to be cluster randomized. Appropriate measures can be taken to avoid and evaluate introduction of bias. Keeping the design simple, practical and with low impact on routine consultations is key.

FUTURE PERSPECTIVES, FURTHER IMPROVEMENT IN DE MANAGEMENT OF CHILDREN WITH RTI IN GENERAL PRACTICE

The keystone for improving future management of children with RTI in general practice is to improve the identification of children who are in need of antibiotic treatment, and of equal importance: identify those who do not. Though extensive research in the past has focused on differentiation between either viral or bacterial pathogens of LRTI, emerging evidence in adults has shown that even patients with bacterial LRTI recover without antibiotics (35), and it might be the group with both viral and bacterial pathogens that profit from most from antibiotic treatment (36). To investigate if this is also true in children will be challenging, but may provide support to counter the paradigm of the child as very vulnerable to serious illness and deterioration without antibiotic treatment.

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Summary

Acute respiratory tract infection (RTI) are common illnesses among children. RTI are mostly self-limiting, with low risk of complications. Only a fraction of the children with RTI present to their GP. For these children, the GP is faced with the task to differentiate between the child with a non-severe infection and the child with a potential severe infection. This distinction then supports the decision whether or not to prescribe antibiotic treatment. This thesis evaluates different aspects of the diagnosis and management of children with RTI in primary care.

Chapter 2 describes the general impact of RTI on children and parents. We asked parents of children with both upper and lower respiratory tract infection who consulted their GP to fill in daily diaries for 14 days after consultation. In total, 149 diaries were included for analysis. The illness related symptoms scored were disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities. These symptoms were all were very common during RTI episodes. Overall, the median time from the first consultation to reported recovery of illness related symptoms in children with URTI was 4 days versus 5 days in children with LRTI. Sleep disturbance persisted most, with a mean duration of 3.1 and 4.3 days for URTI and LRTI, respectively. Respiratory symptoms scored were cough, phlegm, dyspnea, wheezing and nasal congestion. Respiratory symptoms persisted longer than the more general illness symptoms. The median time to reported recovery of respiratory symptoms in children with URTI was 6 days versus 8 days in children with LRTI. 52% Of the children were absent for one or more days from childcare or school, and 28% of mothers and 20% of fathers reported absence from work the first week after GP consultation with their child. Re-consultation occurred in 48% of the children. OTC medication was given frequently to children with RTI, particularly paracetamol and nasal sprays. We believe it is important that GPs appreciate and communicate about the more general burden of disease in children with RTI and their parents.

Identifying a child with pneumonia in the large group of children presenting to a GP with acute RTI is challenging for GPs. Knowledge on the diagnostic value of specific signs and symptoms may guide GPs and aid in development of future decision rules. In **chapter 3** we aimed to identify and systematically review available evidence on the diagnostic value of signs, symptoms and additional tests to diagnose pneumonia in children in an ambulatory setting in developed countries. The original search yielded 4665 records, of which 17 articles were eligible for analysis; twelve studies on signs and symptoms, four on additional laboratory tests and six on ultrasonography. All included studies were performed in a secondary care setting, where prevalence of pneumonia varied from 3.4%-71.7%. Risk of bias was present in the majority of studies in the domain of patient selection. The diagnostic value of the available 27 individual signs and symptoms to identify pneumonia was low. In a low prevalence setting (4 studies, pneumonia prevalence <10%) clinically ill appearance of the child and oxygen saturation <94% can aid a physician. In a high prevalence setting (10 studies, pneumonia >10%) additional diagnostic tests such as oxygen saturation, C-Reactive Protein and White Blood Count are more promising. Chest ultrasonography showed high diagnostic value in settings with

higher prevalence of pneumonia. We concluded that single signs and symptoms from medical history and physical examination or individual additional diagnostic tests are insufficient to diagnose pneumonia in ambulant children. Unfortunately, there are very few diagnostic studies conducted in settings with low prevalence of pneumonia, and no studies from primary care could be included. Future research in low prevalence settings should focus on the diagnostic value of the combination of clinical features and additional testing possibly using meta-analysis of individual data.

C-reactive protein (CRP) is an acute phase protein, synthesized by hepatocytes. After stimulus, serum concentration of CRP rises quickly, with elevated concentrations found after 6 hours, and a peak production after 48 hours. CRP is a sensitive, though non-specific marker of inflammation, infection and tissue damage. CRP levels do not allow differentiation between bacterial or viral origin of an infection in adults or children, but they are proxy for the disease severity. For CRP, a point-of-care test is available. The result of the test is available within four minutes, requiring 1,5µL of blood obtained via finger prick. In adults, point-of-care CRP testing has added value in the diagnosis of pneumonia and safely reduces antibiotic prescriptions for acute respiratory tract infections in primary care. Following this evidence, current guidelines recommend using point-of-care CRP to aid in diagnosis and management of pneumonia in adults. More than half of all Dutch GPs have access to point-of-care CRP testing, in daytime practice as well as at out-of-hours services. This additional diagnostic test is widely accepted by Dutch GPs for adult patients, but GPs' perceptions of its use in children with LRTI were unknown.

In **chapter 4** we describe a qualitative study in which we explored the perceptions of Dutch GPs of the addition of point-of-care CRP testing to the diagnostic evaluation of children, and compared these to their perceptions of use in adults. Analysing eleven semi-structured interviews, we concluded that GPs' perceptions of the addition of point-of-care CRP testing in children with suspected LRTI differ from their perceptions of this in adults. GPs expressed that their management of children with LRTI is primarily based on an assessment of clinical symptoms and characterised by a more cautious approach than in adults, where they are less inclined to watchful waiting. Specifically, and in contrast with adult patients, GPs feared fast and unexpected clinical deterioration of symptoms in children. They reported a 'better safe than sorry' approach in prescribing decisions. They valued reduction of diagnostic uncertainty by point-of-care CRP as less important in children than in adults. In combination with uncertainty towards the exact diagnostic value of point-of-care CRP and usable cut-off values, this led to reservations on implementation of point-of-care CRP for children. Various GPs mentioned they frequently use POCT CRP in adults to convince patients about the low severity of disease and to support their non-prescribing decisions. GPs expressed that they do not need this in children, as they feel less pressured by parents to prescribe antibiotics, and parents understand non-prescribing decisions.

In **chapter 5** we describe the results of a cluster randomized trial in which we assessed whether use of point-of-care CRP by the GP reduces antibiotic prescriptions in children with suspected non-serious LRTI. 309 Children between 3 months and 12 years of age with suspected LRTI were recruited by 148 GPs: 210 children at general practices and 99 at an out-of-hours service. We found no statistically significant reduction in antibiotic prescriptions in the GP use of CRP group (30.9% vs. 39.4%; OR 0.61; 95CI 0.29-1.23). Only the estimated severity of illness was related to antibiotic prescription. Children were more likely to get an antibiotic prescription with increasing CRP level, ranging from 14% in children with a CRP level < 10 mg/L to more than 50% in children with a CRP level > 40mg/L. Point-of-care CRP levels were <10mg/L in 46% of children.
Though we saw a trend towards reduction in antibiotic prescriptions, this was not statistically significant. This may have been in part due to lack of power. Antibiotic prescribing rates were lower than expected in both groups, and the decrease in prescriptions was also less. Combined with the fact that we did not reach our pre-planned sample size, we conclude that it is still uncertain whether using point-of-care CRP could reduce antibiotic prescribing rates in children with suspect LRTI in general practice. A future, larger study is needed to provide more robust evidence.

In **chapter 6** we discuss some practical obstacles that we encountered while performing our randomised clinical trial. In more detail, we discuss why we feel current rules and regulations threaten research with children on low-risk, minimal-burden interventions. We describe the current rules and regulations for conducting research in children in the Netherlands. The need for double informed consent signed by both parents before a child may be included in a trial in the Netherlands is evaluated. Furthermore, the strict application of some regulations enforced by medical ethical committees and universities themselves are evaluated. We suggest that each trial should be judged and applied rules and regulations should be proportionate to the risk and burden of the intervention under evaluation.

Samenvatting

Acute luchtweginfecties bij kinderen komen veel voor. Een acute luchtweginfectie geneest meestal zonder behandeling, met een laag risico op complicatie. Slechts een deel van de kinderen met een acute luchtweginfectie bezoekt de huisarts. Bij deze kinderen moet de huisarts ten eerste het onderscheid weten te maken tussen kinderen met en zonder een ernstige infectie en ten tweede de kinderen met risico op een gecompliceerd beloop identificeren. Dit leidt vervolgens onder andere tot de beslissing om wel of geen antibiotica voor te schrijven. Dit proefschrift evalueert de verschillende aspecten van de diagnose en het management van kinderen met acute luchtweginfecties in de eerste lijn.

Hoofdstuk 2 omschrijft de impact van een luchtweginfectie op kinderen en ouders. We vroegen ouders van kinderen met zowel bovenste als lage luchtweginfecties (BLWI en LLWI) die de huisarts hadden bezocht om gedurende 14 dagen een dagboek bij te houden. In totaal gebruikten we 149 dagboeken voor de analyse. De gescoorde algemene symptomen waren verstoorde slaap, verminderd eten en/of drinken, zich ziek voelen en hinder bij spelen of dagelijkse activiteiten. Deze symptomen waren veel voorkomend tijdens periodes van luchtweginfecties. De mediane duur vanaf het eerste contact met de huisarts tot herstel van deze algemene symptomen was 4 dagen bij kinderen met een BLWI en 5 dagen bij kinderen met een LLWI. Verstoorde slaap duurde het langst, met een gemiddelde duur van 3,1 en 4,3 dagen bij kinderen met respectievelijk een BLWI en LLWI. De gescoorde klachten van de luchtwegen waren hoesten, slijm ophoesten, kortademigheid, piepende ademhaling en neusverstopping. Deze waren langer aanwezig dan de algemene symptomen. De mediane tijd tot herstel van luchtwegklachten in kinderen met BLWI was 6 dagen versus 8 dagen bij kinderen met een LLWI. Tweeënvijftig procent van de kinderen waren een of meerdere dagen afwezig van school of het kinderdagverblijf, en 28% van de moeders en 20% van de vaders rapporteerden afwezigheid van het werk gerelateerd aan de ziekte van hun kind de eerste week na een bezoek aan de huisarts. Achtenveertig procent van de kinderen bezocht de huisarts nogmaals. Vrij verkrijgbare medicatie werd frequent gegeven aan kinderen met een luchtweginfectie, vooral paracetamol en neusspray.

Het is een uitdaging voor huisartsen om het kind met een pneumonie (longontsteking) te onderscheiden binnen de grote groep kinderen die zich presenteert met een acute luchtweginfectie. Kennis van de diagnostische waarde van specifieke symptomen kan de huisarts helpen en kan voor de toekomst belangrijk zijn om klinische beslisregels te formuleren. Het doel van de systematische review in **hoofdstuk 3** was om de waarde van verschillende symptomen en aanvullende onderzoeken voor het diagnosticeren van pneumonie in de ambulante setting te identificeren en beoordelen. Onze zoekstrategie leverde 4665 artikelen op, waarna verdere selectie plaatsvond. Uiteindelijk waren 17 artikelen geschikt voor verdere analyse: twaalf over symptomen, vier over aanvullend laboratoriumonderzoek en zes over echo-onderzoek. Alle geïncludeerde onderzoeken waren uitgevoerd in de tweede lijn waarbij de prevalentie van pneumonie varieerde

van 3,4% tot 71,7%. Het risico op bias was aanwezig bij het merendeel van de studies in het domein van patiëntselectie. De diagnostische waarde voor het identificeren van pneumonie was laag voor de onderzochte 27 symptomen. In een setting met een lage prevalentie (4 studies, prevalentie pneumonie <10%) was een zieke indruk van het kind en een zuurstofsaturatie <94% van diagnostische waarde. In een setting met een hogere prevalentie (10 studies, prevalentie pneumonie >10%) lijken aanvullende testen zoals zuurstof saturatie, CRP en leukocyten aantal meer waarde te hebben. Echo-onderzoek van de longen had een grote diagnostische waarde in een setting met hogere pneumonie prevalentie. We concludeerden dat geen enkel los onderdeel vanuit de anamnese, het lichamelijk onderzoek of aanvullend onderzoek voldoende waarde heeft om de diagnose pneumonie te kunnen stellen bij kinderen in een ambulante setting. Daarnaast is er helaas weinig onderzoek gedaan in settingen waar de prevalentie van pneumonie lager is, zoals de huisartspraktijk. In de toekomst zou onderzoek gefocust moeten zijn om de diagnostische waarde van een combinatie van klinische symptomen en aanvullend onderzoek.

C-reactief proteïne (CRP) is een acutefase-eiwit dat wordt gemaakt door de hepatocyten. Na een stimulus stijgt de concentratie CRP in het bloed snel. Na zes uur kunnen verhoogde waardes gemeten worden, met een piekproductie na 48 uur. CRP is een gevoelige, maar aspecifieke marker voor ontstekingen, infecties en weefselverval. Het is niet mogelijk om op basis van de hoogte van het CRP onderscheid te maken tussen een bacteriële of een virale infectie, maar het is zowel bij volwassenen als bij kinderen een proxy voor de ernst van de ziekte. Voor CRP is een zogenaamde point-of-care test, of sneltest, ontwikkeld. Dit betekent dat de test uitgevoerd kan worden op de plaats waar de patiënt zich bevindt, en het resultaat binnen vier minuten bekend is. Hiervoor moet een vingerprik worden gedaan om de benodigde 1,5µL bloed te verkrijgen. Uit onderzoek blijkt dat CRP bij volwassenen toegevoegde waarde heeft voor het diagnosticeren van pneumonie. Daarbij neemt de hoeveelheid voorgeschreven antibiotica in de huisartspraktijk af zonder dat er meer complicaties zijn. Richtlijnen bevelen aan om de CRP sneltest te gebruiken bij het stellen van de diagnose pneumonie bij een matig zieke volwassene. Meer dan de helft van de Nederlandse huisartsen heeft beschikking over een CRP sneltest, zowel in de eigen praktijk, als op de huisartsenpost. De test wordt inmiddels veel gebruikt door Nederlandse huisartsen, en de meerwaarde lijkt algemeen geaccepteerd. Het was echter niet duidelijk hoe huisartsen aankeken tegen het gebruik van de CRP sneltest bij kinderen met een luchtweginfectie.

In **hoofdstuk 4** beschrijven we een kwalitatieve studie waarin we de kijk van Nederlandse huisartsen op de toevoeging van de CRP sneltest aan de beoordeling van kinderen met een luchtweginfectie onderzochten. We vergeleken hun percepties bij kinderen met hun perceptie op de test bij volwassenen. Gebruikmakend van elf semigestructureerde interviews vonden we dat de kijk op het toevoegen van de CRP sneltest bij kinderen anders was dan bij volwassenen. Huisartsen gaven aan dat het management van kinderen met een lage luchtweginfectie vooral gebaseerd

is op de beoordeling van klinische symptomen, en zich kenmerkt door een wat voorzichtigere aanpak dan het management bij volwassenen. Huisartsen gaven aan minder afwachtend te zijn bij kinderen. In het bijzonder legden zij nadruk op de opvatting dat de klinische situatie bij kinderen sneller en onverwachter dan bij volwassenen kan verslechteren. De huisartsen gaven hierbij aan te kiezen voor een aanpak waarbij zij aan de veilige kant gingen zitten, en niet het risico te lopen dat zij een keer te weinig antibiotica voorschreven. Het verminderen van diagnostische onzekerheid werd gezien als een minder belangrijk thema bij kinderen dan bij volwassenen. In combinatie met twijfels over de exacte diagnostische waarde van de CRP sneltest bij kinderen en onduidelijkheid over de afkapwaardes maakte dat huisartsen terughoudend waren over de implementatie van de CRP sneltest bij kinderen. Als laatste thema bespraken verschillende huisartsen dat zij de CRP sneltest bij volwassenen regelmatig inzetten als ondersteuning van een beslissing om geen antibiotica voor te schrijven. Een lage CRP waarde wordt dan gebruikt om de patiënt ook te overtuigen dat er geen sprake is van een ernstige ziekte, en er dus geen noodzaak is voor antibiotica. Huisartsen gaven aan dat zij de CRP sneltest niet op deze manier wilden inzetten bij kinderen, omdat zij minder druk ervaren van ouders om antibiotica voor te schrijven dan van volwassenen en ouders vaak de beslissing om geen antibiotica voor te schrijven wel accepteren.

In **hoofdstuk 5** beschrijven we de resultaten van een cluster gerandomiseerde studie waarin beoordeeld werd of het toepassen van de CRP sneltest door de huisarts leidde tot minder antibioticavoorschriften voor kinderen met verdenking op de een lage luchtweginfectie. 309 Kinderen, leeftijd tussen de 3 maanden en 12 jaar, werden geïncludeerd door 148 huisartsen: 210 kinderen in de huisartspraktijk en 99 op de huisartsenpost. We vonden geen statistische significant daling in het aantal antibioticavoorschriften als huisartsen de CRP sneltest gebruikten (30.9% vs. 39.4%; OR 0.61; 95CI 0.29-1.23). De geschatte ernst van de ziekte was de enige factor die gerelateerd was aan het voorschrijven van antibiotica. Kinderen met een hogere CRP waarde kregen vaker antibiotica. Bij een CRP waarde < 10 mg/L kreeg 14% van de kinderen antibiotica voorgeschreven, terwijl meer dan 50% van de kinderen antibiotica kreeg voorgeschreven als de CRP waarde > 40mg/L was. De CRP waarde was < 10mg/L bij 46% van de kinderen.
Hoewel we dus wel een trend zagen naar minder antibioticavoorschriften als huisartsen de CRP sneltest toepasten, was dit niet statistisch significant. Dit zou deels veroorzaakt kunnen zijn door een gebrek aan power in de statistische analyse. In zowel de interventie als de controle groep was het aantal antibiotica voorschriften lager dan verwacht, en ook de afname in het aantal voorschriften was minder. In combinatie met een kleiner dan berekende steekproef concludeerden we dan ook dat het nog niet met zekerheid te beoordelen is of het toepassen van de CRP sneltest resulteert in een vermindering van het aantal antibiotica voorschriften voor kinderen met een lage luchtweginfectie in de huisartspraktijk. Een grotere studie is nodig om meer robuust bewijs te verzamelen.

In **hoofdstuk 6** bediscussiëren we een aantal van de praktische obstakels die wij tegenkwamen in het uitvoeren van de gerandomiseerde klinische studie. Specifiek beargumenteren we waarom we denken dat de huidige regels en wetten onderzoek met kinderen in de toekomst in gevaar brengen. In Nederland is in de Wet Medisch Wetenschappelijk Onderzoek (WMO) vastgelegd dat bij onderzoek bij kinderen beide ouders schriftelijk toestemming moeten geven voorafgaand aan deelname. Dit leverde in ons onderzoek in de huisartspraktijk veel praktische problemen op, waardoor minder kinderen konden deelnemen aan het onderzoek. Verder zijn er ook regels opgesteld door medisch ethische commissies en universiteiten zelf voor het uitvoeren van medisch wetenschappelijk onderzoek. We beargumenteren dat bij een onderzoek met weinig impact op het kind en weinig tot geen kans op complicaties beoordeeld zou kunnen worden of wel alle regels strikt moeten worden toegepast. We denken dat het noodzakelijk is om maatwerk te leveren, om in de toekomst onderzoek in de huisartspraktijk bij kinderen te kunnen blijven uitvoeren.

Dankwoord

Met het treintje…

In januari 2013 maakte ik samen met Ruud het plan om op reis te gaan. Omdat we allebei graag in de trein zitten, ontstond het wilde plan om met de trein in 3 maanden letterlijk de wereld rond te reizen. Zogezegd, zo gedaan. Ik vroeg 3 maanden onbetaald verlof aan en zou na de reis starten met het laatste jaar van de huisartsopleiding. Ruud kon ook vrij nemen, alle seinen stonden op groen!

De oplettende lezer ziet hier al een wissel aankomen. In februari hoorde ik dat er een subsidie was toegekend om onderzoek te gaan doen naar het effect van CRP-meting bij kinderen met luchtweginfecties in de huisartsenpraktijk. Een samenwerking tussen de Universiteit Utrecht, Universiteit Maastricht en Saltro huisartsenlaboratorium. Er kwam hierdoor een AIOTHO plek beschikbaar. AIOTHO is een mooi acroniem voor assistent in opleiding tot huisarts en onderzoeker, een soort dubbelfunctie dus, waarbij je huisarts wordt, maar ook mag promoveren. Zo begon nog voor de eerste reis begonnen was, een tweede: een promotie traject. Na een prachtige treinreis rond de wereld, begon ik in september 2013 als AIOTHO.

Op reis door de wondere wereld van de wetenschap ga je natuurlijk niet alleen. De afgelopen jaren hebben heel veel mensen met mij mee gereisd, soms lang, soms maar kort. Ik ben heel blij, dat nu dit proefschrift bijna af is, ik iedereen hiervoor mag bedanken.

Allereerst mijn drie promotoren. Een bijzonderheid, want meestal zijn het er maar twee, maar ik voel me bevoorrecht om dit traject met drie promotoren te mogen afronden!

Prof. Dr. Verheij, beste Theo dank voor jouw rust en vertrouwen. Elk overleg waar ik onrustig of sceptisch aan begon, eindige met dat jij aangaf dat het allemaal wel goed zou komen. Soms voor mijn gevoel misschien wel tegen beter weten in, maar het was altijd fijn om je vertrouwen te hebben. Vriendelijk en laagdrempelig was je altijd bereid om te overleggen over alle aspecten van het onderzoek en mijn proefschrift.

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onder jouw hoede mocht doen in Maastricht, tot de keuze voor het vak van huisarts en tot het afronden van dit proefschrift heb ik je betrokkenheid en bezieling enorm gewaardeerd, en de bezoekjes aan Maastricht waren altijd lichtpuntjes in een soms wat turbulent traject.

Beste Rogier, ook wij kenden elkaar al vanaf mijn wetenschapsstage en uiteindelijk wil ik jou ook wel als de schuldige aanwijzen dat ik aan dit hele promotietraject begonnen ben! Na een leuk hobby project bij Saltro, was jij degene die me tipte over de vacature bij het Julius Centrum en was je ook zo aardig om alvast een mail te sturen om me te introduceren. Een mail die zo positief was dat ik denk dat mijn uiteindelijke sollicitatiegesprek misschien wel tegenviel… Over de jaren heen zijn we gelukkig blijven samenwerken en het was altijd fijn om je feedback op de onderzoeken te mogen ontvangen.

Beste Lidewij, de eerste 3 jaar van mijn traject was ik blij dat ik jou als co-promotor naast me had staan. Jouw ongelofelijke optimisme en energie die doorklonk in elke mail (ongeacht het tijdstip waarop die verstuurd was) en die je ook meebracht naar elk overleg hebben me door de ingewikkelde begintijd van het onderzoek heen gesleept!

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Beste Sanne, ook jou kende ik al van mijn hobby project bij Saltro, en ik heb onze samenwerking altijd als heel prettig ervaren. De hele organisatie van het plaatsen van de CRP-apparaten (samen met Annelies en Lianne natuurlijk) maar ook je inhoudelijke input bij het project waren zeer waardevol.

Beste dokter Balemans, beste Walter, dank voor jouw input als kinderarts. Waardevolle inzichten over het gebruik van CRP, en andere diagnostiek bij de diagnose van luchtweginfecties in de tweede lijn waren belangrijk in de opzet en uitvoering van de onderzoeken in dit proefschrift.

Beste Esther, jij kwam in beeld toen we bedachten dat het zinvol zou zijn om het onderzoek te verreiken met kwalitatieve data. Toen nog redelijk onontgonnen gebied in het kwantitatieve Utrecht, was het een enorme uitdaging om een artikel te schrijven zonder statistische analyses of toch op z'n minst een tabel met baseline karakteristieken. Ik vind het een enorme toevoeging dat we de kwalitatieve onderzoeken hebben kunnen toevoegen aan alle verzamelde data en wil je bedanken voor jouw deskundige begeleiding in het duiden van onze bevindingen.

Beste Alike, hoewel we elkaar natuurlijk vaker zagen op het Julius en bij de overleggen van de infectiegroep, werkten we pas aan het laatste artikel echt samen. Leuk vond ik het om gebruik te maken van jouw expertise op het vlak van luchtweginfecties en antibiotica gebruik en je grote ervaring in het schrijven van artikelen.

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De dataverzameling van het hoofdonderzoek was nog steeds een puinhoop geweest zonder jouw begeleiding, Susan van Hemert. Hoewel de wereld nog niet klaar bleek voor het online invullen van dagboeken, lukte het om te schakelen naar een papieren versie. Dank dat je altijd snel en kundig antwoord gaf toen de data opgeschoond en verwerkt moest worden!

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Nynke, zorgeloos kon ik zes maanden terug naar de huisartsopleiding wetende dat jij de boel wel draaiende zou houden! Dank daarvoor.

Wesley, vanuit Maastricht heb jij veel werk verzet voor de systematische review in dit proefschrift. Het doorploegen van alle titels en abstracts was een tijdrovend werkje, wetend dat ik jou daarin als tweede reviewer had was erg prettig.

Gedurende alle jaren die dit traject geduurd heeft, heb ik het geluk gehad om altijd een werkplek te hebben op kamer 5.122. Ik wil graag alle lieve kamergenoten bedanken voor hun interesse in mijn traject, maar ook in mij als persoon. Het was altijd fijn om even weer bij te kunnen kletsen als ik een keertje op het Julius was.

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Ik was geen doorsnee huisarts in opleiding, en mijn traject heeft veel aanpassingen gekend. Ik wil graag de SBOH bedanken, dat zij promotietrajecten logistiek en financieel ondersteunen. Daarnaast wil ik de huisartsopleiding Utrecht bedanken, in het bijzonder Roger Damoiseaux en Liesbeth Reinierse, voor het goedkeuren van en steeds weer meedenken bij mijn traject.

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Lieve Karen, jij bent voor mij een voorbeeld in doorzettingsvermogen en vertrouwen op je eigen kracht. Ik ben blij dat wij telkens op het einde van een gezellige bijklets-sessie gelijk weer een nieuwe plannen.

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Liefste Max en Kries. Ik ben bang dat dit proefschrift niet af is dankzij jullie, maar ondanks jullie. Met z'n tweeën zijn jullie de beste afleiding van zogenaamde serieuze zaken als werk en wetenschap. Jullie verwonderen je over de meest kleine dingen en veranderen daarmee mijn kijk op het leven. Ik hoop dat jullie het enthousiasme om *waarom?* als reactie te geven op werkelijk alles, een leven lang vast blijven houden.

"The important thing is not to stop questioning.
Curiosity has its own reason for existing."
Albert Einstein

Curriculum Vitae

Marjolein Schot was born on April 8th 1984 in Oss, the Netherlands. She grew up here as daughter of Peter and Corry Schot, as the middle sister between Willemijn and Eva. At the age of 11 the family moved to the United States for a period of three years. After returning to the Netherlands, Marjolein completed secondary school at Maasland College in Oss. In 2002 she moved to Maastricht to start medical training at the Maastricht University. Graduating cum laude in 2008, she worked at the Máxima Medisch Centrum in Veldhoven, the Wilhelmina Children's hospital in Utrecht and the Wever nursing homes in Tilburg before starting her GP training at Utrecht University in 2011.

In 2013 she continued her GP training as so called AIOTHO, combining the clinical work as GP trainee with a PhD project under supervision of prof. dr. Th.J.M. Verheij, prof. dr. N.J. de Wit and prof. dr. J.W.L. Cals. Alternating research, clinical work and maternity leave she finished her GP training in 2016 after which she has been working as a GP mainly at the general practice Mondriaanlaan in Nieuwegein. After her PhD defense, the focus professionally will be on clinical work in the GP practice, now within general practice d'n Iemhof in Oss.

During the course of the PhD project Marjolein and Ruud became proud parents of Max and Kries, and have recently returned to their roots in Brabant, living in their new home in Berghem.