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Prescribing Antibiotics for Children with Acute Infections in Latvian Primary Care and Effects of Multifactorial Intervention

Summary of the Doctoral Thesis for obtaining
the scientific degree "Doctor of Science (*PhD*)"

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Sector – Clinical Medicine

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Abbreviations used in the Thesis

AB	antibiotics
aOR	adjusted odds ratio
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C reactive protein
IQR	interquartile range
FBC	full blood count
GABHS	group A β haemolytic streptococcus
GP	general practitioner
POCT	point-of-care testing
GI	gastrointestinal infections
OR	Odds ratio
R	randomisation
RI	respiratory infections
SD	standard deviation
UTI	urinary tract infections

Introduction

Antimicrobial resistance is a global healthcare problem that poses a major threat to public health and is one of the leading causes of morbidity and mortality worldwide (1). Based on data from over 200 countries, it has been estimated that approximately 4.95 million deaths annually are associated with antimicrobial resistance, with 1.27 million of these attributable directly to drug-resistant infections (2). The development of antimicrobial resistance is directly associated with the excessive and inappropriate prescribing and use of antibiotics (2–4). The development and availability of new antibiotics are slow and insufficient, particularly for paediatric patients, making it crucial to explore ways to optimize the rational use of currently available antibiotics. (5, 6).

General practice accounts for around 90 % of all antibiotic prescriptions, 30–50 % of antibiotics prescribed in out-patient settings are considered to be unnecessary or inappropriate (7, 8), particularly among paediatric and elderly patients (9). The most frequent indication for antibiotic use in children is upper respiratory tract infection, with the highest incidence observed in infants and preschool-aged children, despite the predominance of viral, self-limiting aetiology in this age group, for which antibiotic therapy is not indicated. (10, 11). European studies indicate that by the age of one, approximately 50 % of children have received at least one course of antibiotic therapy (12, 13) and one of four children antibiotics are prescribed by their general practitioner at least once a year (14).

The main drivers of overprescription are difficulties differentiating between viral and bacterial diseases based on clinical signs alone (15). Although it is well established that viral infections predominate in childhood, their clinical manifestations are often non-specific (5). General practitioners' fear of missing serious bacterial infections and potential complications often leads to the early initiation of antibacterial treatment and the use of broad-spectrum antibiotics (8, 15, 16).

Rational decisions about antibiotic prescribing are based on a proper diagnosis (17). Over the past decades, point-of-care testing (POCT) has assumed an increasingly important role in primary care (18, 19). These are rapid, minimally invasive, and user-friendly diagnostic tests that can be easily performed during a patient visit, providing immediate results and enabling physicians to better justify both the diagnosis and treatment decisions, including reducing unnecessary antibiotic prescriptions. Examples include rapid tests for group A beta-haemolytic streptococcus (GABHS), urine dipsticks, and, more recently, point-of-care measurement of C-reactive protein (CRP) in capillary blood (20, 21).

The availability and use of POCT varies substantially not only between countries but also among individual practices within the same country (21). In Europe, POCT are widely used in countries such as Denmark, the Netherlands, and Norway, whereas their use in routine clinical practice remains minimal in Belgium and Greece (16). The most commonly used tests are GABHS rapid testing and urine dipsticks (21). Similarly, data from Latvia in 2010 show that POCT were rarely used in primary care prior to initiating antibiotic treatment, and diagnostic decisions were predominantly based on variable clinical signs (22).

CRP is a non-specific inflammatory marker that is widely used to assess the severity of infection and the likelihood of bacterial disease (23), and in recent years it has been more introduced as a point-of-care test (POCT) in primary care in several countries. (23–25). In Latvia, CRP POCT is minimally used, being implemented in only a few general practices. CRP POCT is a minimally invasive, rapidly performed, and validated test, the effectiveness of which in reducing antibiotic use among adult patients with lower respiratory tract infections has already been demonstrated (24, 26, 27), and it is included in the National Institute for Health and Care Excellence (NICE) guidelines (28). In paediatric patients, evidence regarding the effectiveness and safety of CRP POCT in reducing antibiotic use remains limited and inconclusive (29), which limits its broader implementation in clinical practice. The effectiveness of combining GP education with the introduction of CRP POCT on antibiotic prescribing and diagnostic practices has not yet been evaluated in the paediatric population.

Aim of the Thesis

The aim of this thesis is to assess antibiotic prescribing and diagnostic practices in children with acute infections in primary care in Latvia, and the impact of multifactorial interventions (GP education and the use of CRP POCT), as well as the long-term effects of educational interventions on changes in these practices.

Objectives of the Thesis

The following objectives have been set to achieve the aim of the doctoral thesis:

1 To investigate antibiotic use in children with acute infections in primary care, identify the most common infections for which GPs prescribe antibiotics, and analyse the types of antibiotics used, as well as the associations between various patient and GPs factors and antibiotic prescribing.

2 To implement and evaluate the impact of multifactorial interventions (GP education combined with the availability of CRP POCT), as well as the long-term effects of educational interventions, on antibiotic prescribing practices in children with infections in primary care.

3 To analyse the diagnostic process prior to antibiotic prescribing and to assess the effect of the study interventions on it.

4 To evaluate the measurement of the inflammatory marker CRP and the interpretation of its results prior to decisions regarding the initiation of antibiotic therapy.

Hypotheses of the Thesis

1 Antibiotics are often prescribed early and frequently for potentially self-limiting viral infections, with decisions to initiate therapy predominantly based on variable clinical signs rather than supported by diagnostic testing.

2 GP education combined with the use of CRP POCT reduce antibiotic prescribing, increase the use of diagnostic testing prior to treatment decisions, and decrease the prescription of broad-spectrum antibiotics in children with acute infections.

Scientific novelty of the Thesis

1 Antibiotic prescribing practices in the paediatric population within primary care have, to date, been insufficiently studied in Latvia. The 2013 "Happy audit" (30), which included both paediatric and adult patients, highlighted the need for targeted education of general practitioners on rational antibiotic prescribing.

2 This study explores the role of CRP POCT, which have been minimally used in Latvia, together with general practitioner education in guiding decisions regarding antibiotic prescribing. To date, no intervention studies in Latvia have specifically addressed educational and diagnostic strategies aimed at reducing antibiotic use in primary care, with particularly limited data available for the paediatric population.

3 Recent studies have shown that the use of CRP POCT significantly reduces antibiotic prescribing in adults with lower respiratory tract infections. However, data on its effectiveness in guiding antibiotic prescribing for children remain limited and controversial, and further investigation is required.

1 Materials and methods

1.1 Study design

The study was conducted as randomized controlled intervention study in primary care in Latvia and consisted of two periods from November 2019 to April 2021. The study design is schematically presented in Figure 1.1. A total of 80 general practitioners (GP) were randomly assigned into two groups. In the first period, the first group of GPs (Group A) received a combined intervention (GP educational intervention and availability of CRP POCT in practice), whereas the second group of GPs (Group B) continued their usual care without interventions and served as the control group. Patient enrolment in both groups was performed according to predefined inclusion and exclusion criteria.

After three months, a two-week crossover occurred: GPs from Group B received the combined intervention (educational intervention and CRP POCT availability) in the second period, while Group A continued usual care without CRP POCT availability. It should be noted that Group A no longer served as a control group in the second period, as they had already received the educational intervention, which could influence antibiotic prescribing practices. The long-term education effect was evaluated in this group. Consequently, the study results were analysed across three groups:

1 Combined intervention group (Group A in phase one and Group B in phase two)
2 Usual care group (Group B in phase one)
3 Long-term education group (Group A in phase two)

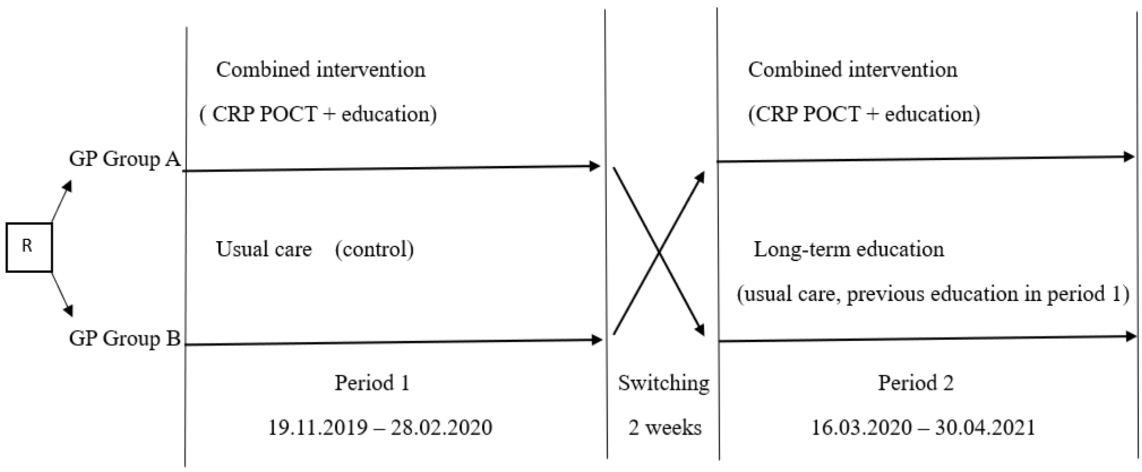

Figure 1.1 **Study overview**

GP – general practitioner, R – randomization, CRO POCT – C reactive protein point-of-care test

1.2 Participating family physicians

A total of 80 GPs from various regions of Latvia were included in the study (Figure 1.2). Among them, 35 GPs were from Riga and the surrounding region, 21 from regional cities, and 24 from rural areas.

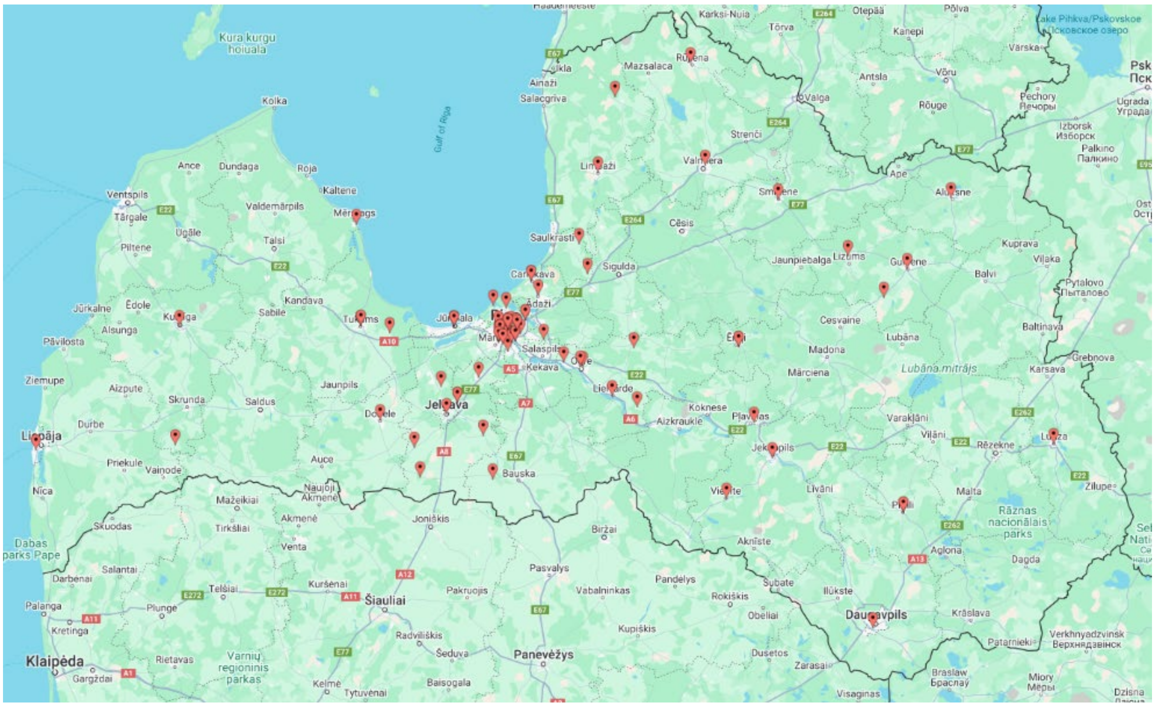

Figure 1.2 **Distribution of the 80 general practitioners included in the study across Latvian regions**

The progression of general practitioners' participation in the study is illustrated in Figure 1.3. Following randomization, five GPs withdrew from the study (two from the Riga region, two from the Kurzeme region, and one from the Zemgale region), leaving 75 GPs to continue. During the second phase, two further GPs withdrew (one from the Kurzeme region and one from the Latgale region).

1.3 Participating children

Inclusion criteria: children aged 1 month to 17 years attending a face-to-face visit with a general practitioner for an acute infection, presenting with symptoms lasting less than five days, were included in the study.

Exclusion criteria:

1 Patients in the recovery phase.

2 Patients who had already started antibiotic therapy prior to the visit.

3 Complaints lasted more than five days.

The patient flow is shown in Figure 1.3. A total of 3,801 patients were initially enrolled. Of these, 484 patients were excluded due to not meeting the inclusion criteria or due to incomplete data. Ultimately, 3,317 patients were included in the analysis (886 in the control group, 1,784 in the combined intervention group, and 647 in the long-term education group).

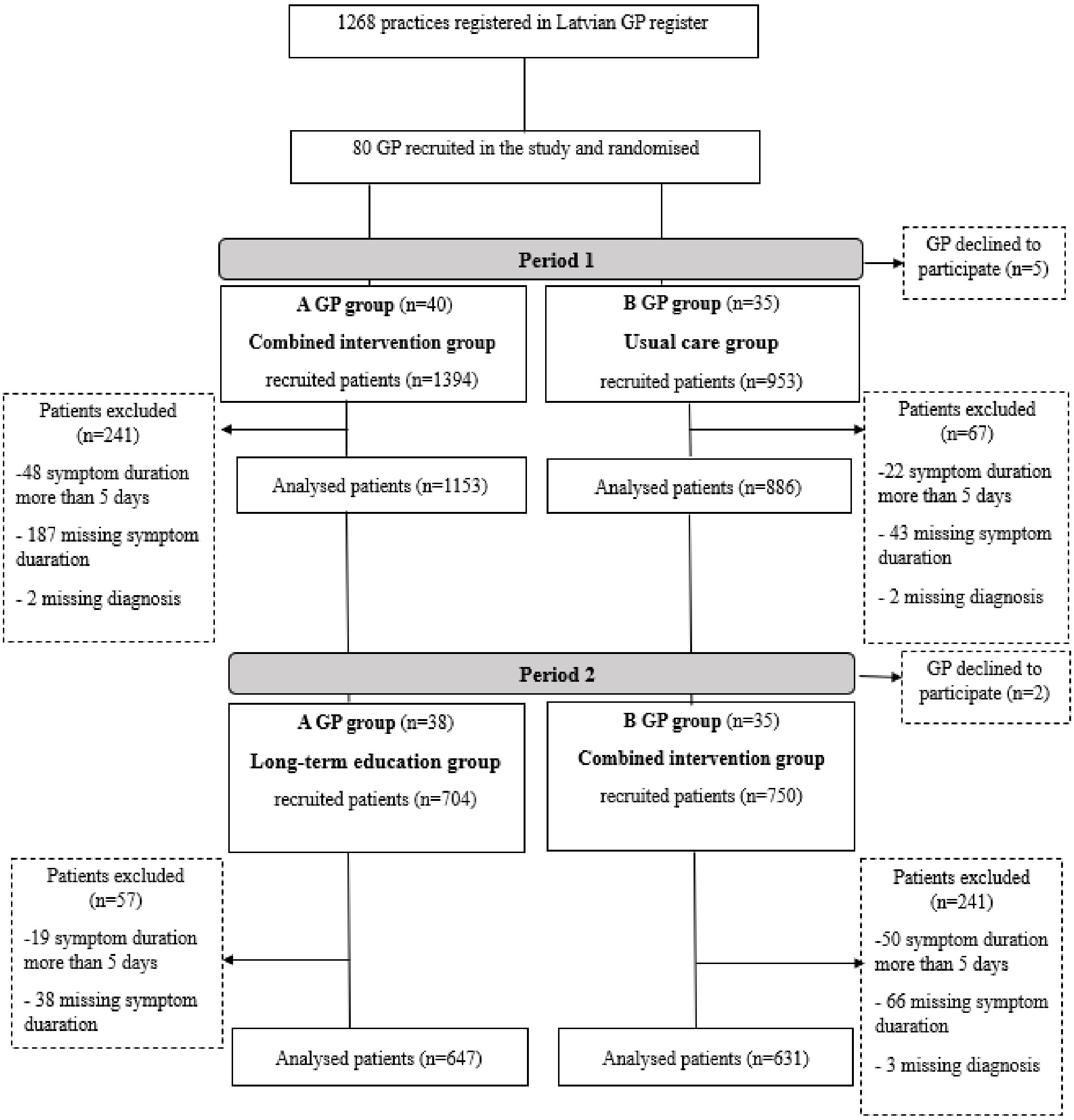

Figure 1.3 **Flowchart of the study's recruitment process**

GP – general practitioner

1.4 Interventions

GPs groups according to the presence of intervention were combined for analysis as follows:

1 Combined intervention group: GPs received a CRP POCT device for use in routine practice along with an educational intervention.

2 Control group: GPs continued their usual practice.

3 Long-term education group: GPs had received the combined intervention (CRP POCT device and educational intervention) in the previous period and, drawing on

the knowledge and experience gained, continued routine practice without CRP POCT availability.

1.4.1 CRP POCT availability in general practitioners' practices

We used the Orion Diagnostica QuikRead go CRP POCT system for the quantitative determination of CRP in blood with a sample volume of 20 µl obtained via a finger prick. This system has a measuring range of 5–200 mg/L and the result is available within 2 minutes.

General practitioners were trained in the use of the CRP POCT device through individual on-site visits in their practices, conducted by an expert from the CRP POCT manufacturing company. During the training, GPs were introduced with the manufacturer's recommendations for CRP POCT result interpretation, which are based on studies in adult patients with lower respiratory tract infections (Table 1.1). However, they were informed that currently, there are no standardized threshold values for paediatric age group defined for the interpretation of the test results, and therefore such guidelines were not provided to study participants (29, 31).

Table 1.1

CRP thresholds for adults presenting symptoms of LRTIs

CRP level	Evaluation	Recommendation
< 20 mg/L	Self-limiting infection	Do not prescribe antibiotics
20–40 mg/L	Mostly self-limiting infection – evaluate specific patient risk	Do not prescribe antibiotics for low-risk patients Consider delayed prescription
41–100 mg/L	Clinical picture most deciding – evaluate specific patient risk	Consider starting antibiotics for patients with comorbidities that increase risk of complications (COPD, diabetes, elderly)
> 100 mg/L	Severe infection	Start treatment with antibiotics Consider hospital referral

Van Hecke et al. 2023. Guidance on C-reactive protein point-of-care testing and complementary strategies to improve antibiotic prescribing for adults with lower respiratory tract infections in primary care. Front. Med., 10. doi: 10.3389/fmed.2023.1166742 (27).

GPs were allowed to order a CRP test based on individual indications if they believed the result would help them make a more informed decision on antibiotic necessity after a clinical assessment. The use of other available tests in the practice or those performed in central laboratories was not restricted and could be ordered according to the physician's clinical assessment.

1.4.2 General practitioners' education intervention

The educational intervention was conducted as one five-hour training seminar, followed by educational materials in video and printed format. The seminar provided training to general practitioners on the following topics:

- principles of antibiotic resistance and safer prescribing of antibiotics,

- child with fever – clinical evaluation, precautionary level system, diagnostics and treatment and also recommendations for parents (recommendations introduced in Latvia in 2019),
- child with upper and lower respiratory infection – the evaluation of patients with acute epiglottitis, laryngitis, bronchiolitis, and pneumonia, diagnostic investigations, treatment strategies, and guidance for parents (recommendations introduced in Latvia in 2019).

1.5 Data collection

In both study periods GPs recorded data in anonymized, specially designed questionnaires developed for the study, available in both electronic and paper formats, which included patient's demographic data, diagnostic tests undertaken prior to the initiation of antibiotic treatment, decision on antibiotic treatment and referral to hospital or ambulatory care. Study data were collected in a database created in Microsoft Excel program.

1.6 Ethics statement

The study was approved by the Research Ethics Committee of Rīga Stradiņš University, approval no. 6–3/5/21 (received: 30 May 2019).

1.7 Statistical analyses

All data were recorded in Microsoft Excel and analysed using IBM SPSS Statistics, version 23.0. For nominal variables, frequencies (n) and percentages (%) were reported.

The conformity of continuous variables to a normal distribution was tested using the Kolmogorov-Smirnov test. Descriptive statistics, such as means (with standard deviations (SD)) and medians (with interquartile range (IQR)) for continuous variables were calculated. The Chi-square Test or Fisher's Exact Test was used to determine the statistical significance of differences in the proportions of dependent variables between subgroups of independent variables, whereas for continuous variables – the Kruskal-Wallis Test and Mann-Whitney Test were used.

Univariate and multivariate binary logistic regression analyses were performed to identify general practitioner- and patient-related factors associated with antibiotic prescribing and CRP testing. Since multiple patients were recruited from each general practitioner's practice according to the study design, potential clustering of observations within practices was also considered.

To account for this the associations were also tested using a generalised linear mixed model with a binomial distribution (mixed effects logistic regression model), allowing for the hierarchical structure of the data to be modelled (32, 33). Both GP-related and patient-related factors, as well as the study intervention, were included as fixed effects, but GPs' identification numbers as random effect. The extent of the clustering effect at the general practitioner level was evaluated using the variance partition coefficient (VPC), which quantifies the proportion of overall variability in antibiotic prescribing that can be attributed to differences between GP practices (34).

Several models were fitted to assess potential interactions between the study interventions and other variables. A particularly notable interaction was observed regarding the effect of the interventions on the ordering of diagnostic tests, depending on the GP practice location or the availability of rapid access to laboratory test results. In these cases, a stratified analysis was conducted, evaluating the effects of the interventions separately within each GP practice subgroup.

Results were considered statistically significant at $p < 0.05$. Graphical representation of the results was produced using SPSS and Microsoft Excel.

2 Results

2.1 General demographic data of study participants (general practitioners) and characteristics of GP practices

The mean age of the GPs was 51.9 years, and the majority of participants were women (97.3 %). Their professional experience ranged from 1 to 52 years. The number of registered children in their practices varied widely, from 48 to 1,843 paediatric patients. Two participants were outpatient paediatricians.

2.1.1 Availability of diagnostic tests in practices

To assess the availability of laboratory tests among the participating general practitioners, they were asked to complete a pre-study questionnaire about their practice. 53.3 % (n = 40) reported receiving laboratory results within the same working day, 45.3 % (n = 34) the following working day, and one GP indicated results were received within 2 working days or longer. Turnaround times were longer if the patient visit occurred on a Friday or during the weekend.

Sixty-seven GPs provided more detailed information regarding available tests and their routine approach to different diagnoses. In daily practice, 59.7 % (n = 40) of GPs based their antibiotic prescribing decisions solely on clinical signs without additional diagnostic testing for acute pharyngotonsillitis, 37.3 % (n = 25) for acute bronchitis, 50.7 % (n = 34) for pneumonia, 38.8 % for acute cystitis, and 35.3 % for acute pyelonephritis.

Regarding the availability of POCT in their practices, 62.7 % (n = 42) had a rapid streptococcal antigen test (AGBHS), 59.7 % (n = 40) had urine dipsticks, and 17.9 % (n = 12) had rapid influenza tests.

2.1.2 Characteristics of general practitioners according to the study groups

A general comparison of GP characteristics between the study groups – A and B – is presented in Table 2.1. Data from 40 GPs were analysed in Group A and 35 GPs in Group B, as five GPs withdrew from the study after randomization.

There were no significant differences between the study groups regarding the age, sex and work experience of the GP or number of registered paediatric patients. The distribution of practice locations was similar across groups.

Table 2.1

Characteristics of family physicians according to the study groups A and B

Variables	Group A (n = 40)	Group B (n = 35)	p value
Age (years)			
Median (IQR)	52.5 (46.3–59.8)	53.0 (46.0–61.0)	0.90
Gender			
Male, n (%)	1 (2.5)	1 (2.9)	0.99
Female, n (%)	39 (97.5)	34 (97.1)	
Work experience (years)			
Mean (SD)	25.4 (13.1)	24.6 (11.9)	0.78
Proportion of children on patient list (%)			
Median (IQR)	24.3 (16.7–43.4)	24.2 (16.9–38.1)	0.87
Location			
Rural, n (%)	14 (35.0)	10 (28.6)	0.75
Regional cities, n (%)	10 (25.0)	8 (22.9)	
Capital of Latvia, n (%)	16 (40.0)	17 (48.6)	

2.2 General demographic characteristics of patients

A total of 3,317 patients were included in the data analysis. The median age was 4.0 years (IQR 2.0–8.0). Approximately half of the patients were young children aged 1 month to 4 years (n = 1,686, 50.8 %). The age distribution of the patients is shown in Figure 2.1. Age data were missing for 31 patients.

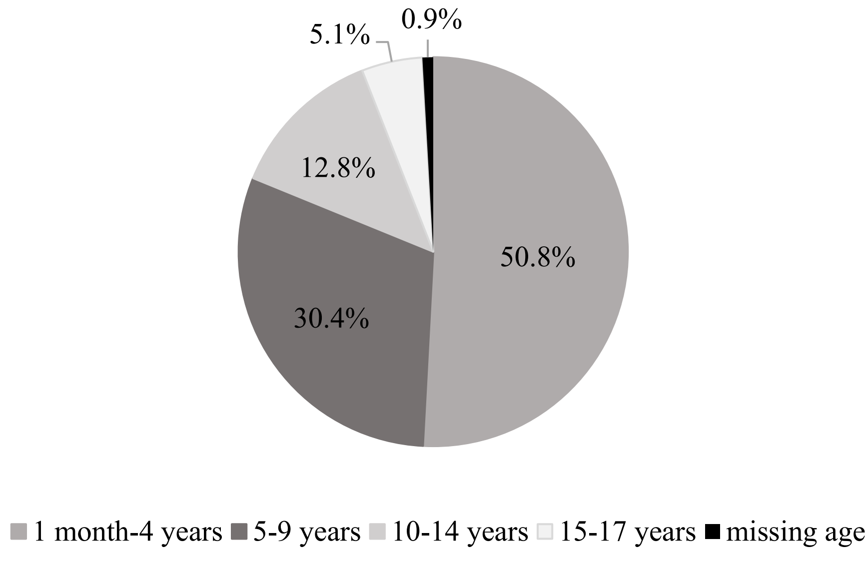

Figure 2.1 **Patient age**

The distribution of boys and girls was nearly equal (50.7 % boys, 49.3 % girls). The median duration of symptoms was 3 days (IQR 2.0–4.0). The distribution of patients by symptom duration is shown in Figure 2.2.

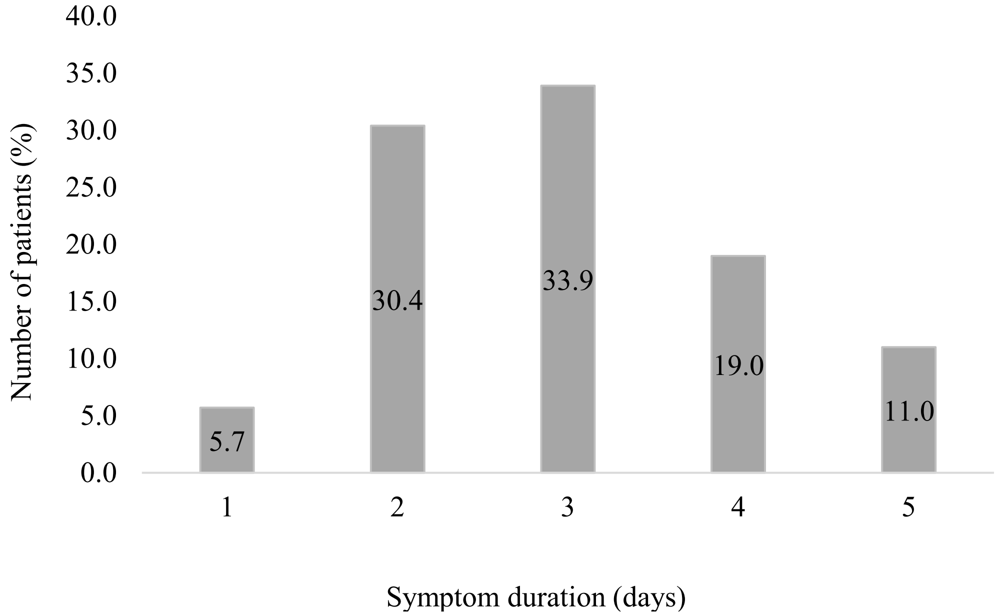

Figure 2.2 **Distribution of patients by symptom duration**

Chronic comorbidities were reported in 8.2 % of the included patients (n = 271). The most common condition was bronchial asthma (n = 223, 85.1 %). Less frequent comorbidities included chronic urinary tract infections (n = 14, 5.3 %), congenital heart disease (n = 7, 2.7 %), juvenile idiopathic arthritis (n = 6, 2.3 %), and other conditions such as neutropenia, diabetes mellitus, vasculitis, cystic fibrosis, and human immunodeficiency virus infection (n = 12, 4.6 %).

Out of 3,245 patients with available vaccination information, 93.2 % (n = 3023) were vaccinated according to the Latvian immunization schedule for their age, 5.8 % (n = 189) were partially vaccinated, and 1.0 % (n = 33) were unvaccinated.

The majority of patients visited their GP due to respiratory infections (n = 3171, 95.6 %), of which 76.8 % (n = 2546) were upper respiratory tract infections and 18.8 % (n = 625) – lower respiratory tract infections. Patients with gastrointestinal infections, urinary tract infections, skin and soft tissue infections, and bone and joint infections were considerably less frequent. The observed infection sites are presented in Table 2.2. In the study results, when analysing changes in diagnostic testing practices and CRP interpretation (subsections 2.6 and 2.8), respiratory infections were divided into diagnostic subgroups (see Table 2.2), whereas other infection sites were not further subdivided due to the small number of patients.

Table 2.2

Infection locations in the study population

Diagnoses		n	% in diagnoses subgroups	% total
Upper respiratory infections		2546	N/A	76.8
Diagnoses subgroups	Otitis	223	8.8	N/A
	Rhinosinusitis	244	9.6	N/A
	Pharyngotonsillitis	737	28.9	N/A
	Other upper respiratory infections	1342	52.7	N/A
Lower respiratory infections		625	N/A	18.8
Diagnoses subgroups	Pneumonia	91	14.6	N/A
	Bronchitis, bronchiolitis	534	85.4	N/A
Gastrointestinal infections		73	N/A	2.2
Urinary tract infections		49	N/A	1.5
Skin and soft tissue infections		20	N/A	0.6
Bone and joint infections		4	N/A	0.1

N/A – not applicable

Most patients continued outpatient care after the GP visit (98.4 %, n = 3.264), while only 53 patients (1.6 %) were referred for hospitalization.

2.2.1. Characteristics of patients according to the study groups

Patient data were compared across the three study groups (Table 2.3): the usual care group (n = 886), the combined intervention group (n = 1.784), and long-term education group (n = 647). The long-term education group included a proportionally higher number of young children aged 1 month to 4 years, as well as patients with urinary tract and skin/soft tissue infections, and more patients were referred for hospitalization. Conversely, children in this group had proportionally fewer chronic conditions and were more often fully vaccinated compared with the usual care group.

Table 2.3

Characteristics of patients according to study groups

Characteristics		Combined intervention group (n = 1784)	Usual care group (n = 886)	Long-term education group (n = 647)	p value
Age (years)					
Median (IQR)		5.0 (2.0–9.0) a	5.0 (2.0–8.0) b	3.0 (2.0–6.0) ab	**< 0.001**
Age group, n (%)	1 months–4 years	839 (47.6) abc	435 (49.7 %) def	412 (63.8) abcdef	**< 0.001**
	5–9 years	569 (32.3) a	279 (31.8 %) d	159 (24.6) ad	
	10–14 years	249 (14.1) b	120 (13.7 %) e	57 (8.8) be	
	15–17 years	107 (6.1) c	42 (4.8 %) f	18 (2.8) cf	

Table 2.3 continued

Characteristics	Combined intervention group (n = 1784)	Usual care group (n = 886)	Long-term education group (n = 647)	p value
Sex				
Boys	865 (48.8)	440 (50.0)	318 (49.5)	0.84
Girls	907 (51.2)	440 (50.0)	325 (50.5)	
Duration of illness (days)				
Median (IQR)	3.0 (2.0–4.0) ab	3.0 (2.0–4.0) a	3.0 (2.0–4.0) b	**< 0.001**
Comorbidities				
Yes	126 (7.1) a	102 (11.5 %) ab	43 (6.6) b	**< 0.001**
No	1658 (92.9) a	784 (88.5 %) ab	604 (93.4) b	
Vaccination				
Full vaccination	1623 (92.9) a	820 (95.0 %) abc	580 (91.3) bc	**0.03**
Partial vaccination	105 (6.0)	40 (4.6) b	44 (6.9) b	
No vaccination	19 (1.1) a	3 (0.3) ac	11 (1.7) c	
Location of infection				
Upper respiratory	1376 (77.1) ab	675 (76.2) gh	495 (76.5) abgh	**< 0.001**
Lower respiratory	337 (18.9) cd	180 (20.3) ij	108 (16.7) cdij	
Gastrointestinal	41 (2.3) ef	19 (2.1) k	13 (2.0) efk	
Urinary tract	20 (1.1) ace	10 (1.1) gi	19 (2.9) acegi	
Skin and soft tissue	8 (0.4) bdf	1 (0.1) hjk	11 (1.7) bdfhjk	
Bones and joints	2 (0.1)	1 (0.1)	1 (0.2)	
Management				
Ambulatory patients	1756 (98.4)	879 (99.2) a	629 (97.2) a	**0.009**
Referred to hospital	28 (1.6)	7 (0.8) a	18 (2.8) a	

a, b, c, d, e, f, g, h, I, j, k – two-by-two tables earmarked where statistically significant differences have been found.

2.3 Antibiotic prescribing in the study population

Overall, 29.3 % of the study patients (n = 972) received antibacterial treatment. Of these, 79.7 % (n = 775) received an immediate prescription, while 20.3 % (n = 197) were issued a delayed prescription. A delayed prescription was defined as a case in which the GP provided the prescription during the visit but advised the patient to initiate therapy only if their general condition worsened over time.

A total of 93.8 % (n = 912) of antibiotics were prescribed for respiratory infections – 62.2 % (n = 605) for upper respiratory tract infections and 31.6 % (n = 307) for lower respiratory tract infections – while only 6.2 % (n = 60) were prescribed for other acute conditions (Figure 2.3).

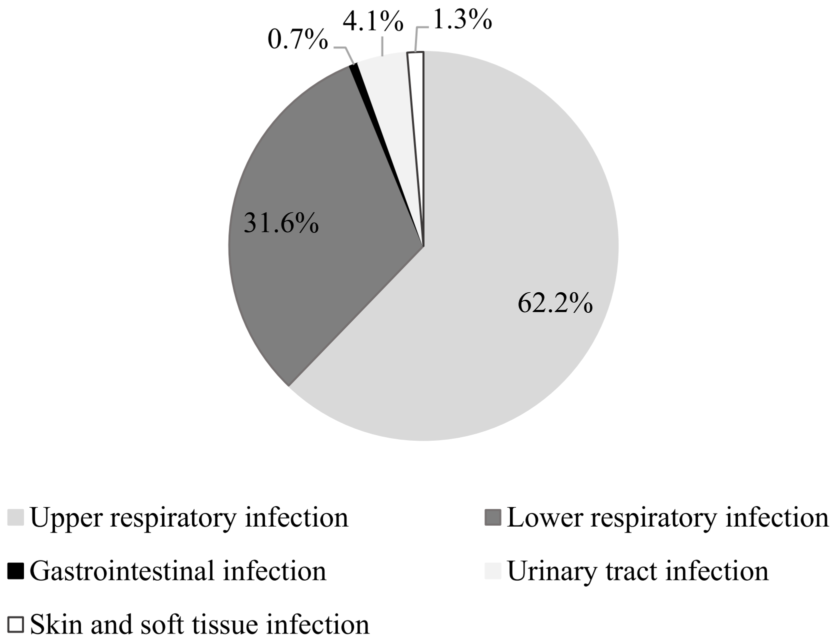

Figure 2.3. **Prescribed antibacterial treatment according to infection location**

2.3.1 Immediate and delayed antibiotic prescribing according to infection location

Antibiotics were prescribed for 23.7 % (n = 605) of patients with upper respiratory tract infections and 49.1 % (n = 307) of patients with lower respiratory tract infections. Proportionally, antibiotics were more frequently prescribed for patients with urinary tract infections – 81.6 % (n = 40) and skin and soft tissue infections – 65.0 % (n = 13); however, these patient groups were considerably smaller than those with respiratory infections. Among four patients with bone and joint infections, no antibiotics were prescribed. Delayed prescriptions were more commonly used for patients with lower respiratory tract infections – 10.1 % (n = 63) and skin and soft tissue infections – 15.0 % (n = 3). Immediate and delayed antibiotic prescribing according to infection location is shown in Figure 2.4.

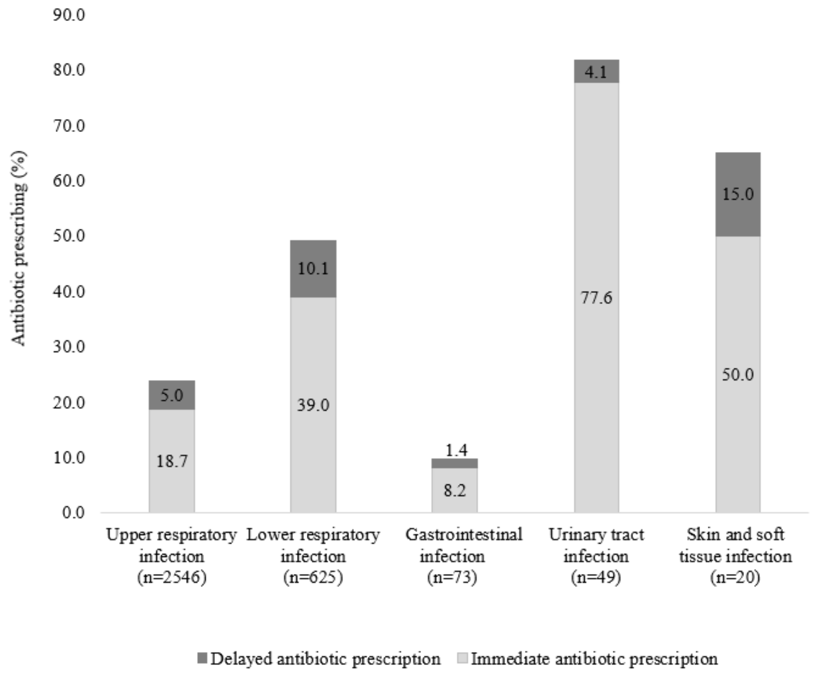

Figure 2.4 **Proportion of patients (%) treated with antibiotics (immediate or delayed prescription) in each infection location**

2.3.2 Immediate and delayed antibiotic prescriptions according to duration of symptoms

Overall, there was a tendency to prescribe antibiotics more frequently in patients with a longer duration of symptoms; however, 19.0 % of patients received antibiotics on the first day of illness, and 25.8 % on the second day. Delayed prescriptions were rarely issued on the first day of illness, but their use increased from the second to the fourth day. Immediate and delayed antibiotic prescribing according to the day of illness is shown in Figure 2.5.

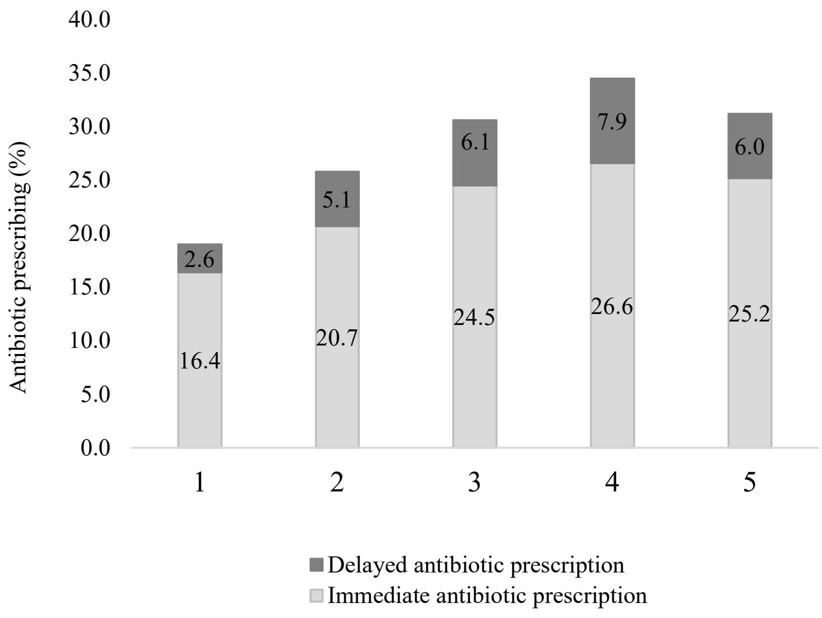

Figure 2.5 **Proportion of patients (%) receiving immediate or delayed antibiotic prescription according to duration of symptoms**

2.3.3 Narrow- and broad-spectrum antibiotic prescribing according to infection location

The classification of antibiotics was based on the Anatomical Therapeutic Chemical (ATC) classification system (Class J01)(127). According to this, the groups recorded in the study included: beta-lactamase-sensitive penicillins (J01CE, e.g., phenoxymethylpenicillin), broad-spectrum penicillins (J01CA, e.g., amoxicillin, ampicillin), penicillins with beta-lactamase inhibitors (J01CR, e.g., amoxicillin/clavulanic acid), macrolides (J01FA, e.g., clarithromycin, azithromycin), first-, second-, and third-generation cephalosporins (J01DB, e.g., cefazolin, cefadroxil; J01DC, e.g., cefuroxime, cefprozil; J01DD, e.g., ceftriaxone), sulphonamides/trimethoprim (J01E), nitrofurans (J01XE, e.g., nitrofurantoin, furagin), and other antibiotics recorded only in isolated cases (e.g., rovamycin, ciprofloxacin).

Following previous publications (128), narrow-spectrum antibiotics were defined as beta-lactamase susceptible penicillins (J01CE), broad-spectrum penicillins (J01CA), first-generation cephalosporins (J01DB), and nitrofurans (J01XE). Broad-spectrum antibiotics were defined as penicillins with beta-lactamase inhibitors (J01CR), macrolides (J01FA), second- and third-generation cephalosporins (J01DC, J01DD), sulphonamides/trimethoprim (J01E), and others (e.g., rovamycin, ciprofloxacin).

Figure 2.6 shows the selection of narrow- and broad-spectrum antibiotics according to infection location. Overall, 67.8 % (n = 632) of prescribed antibiotics were narrow-spectrum, while 32.2 % (n = 300) were broad-spectrum. For 40 patients, antibiotics were prescribed, but the specific agent was not indicated. The most frequently used antibiotics were amoxicillin (J01CA) (53.9 %, n = 524), amoxicillin/clavulanic acid (J01CR) (14.9 %, n = 145), and macrolides (J01FA) (10.1 %, n = 98).

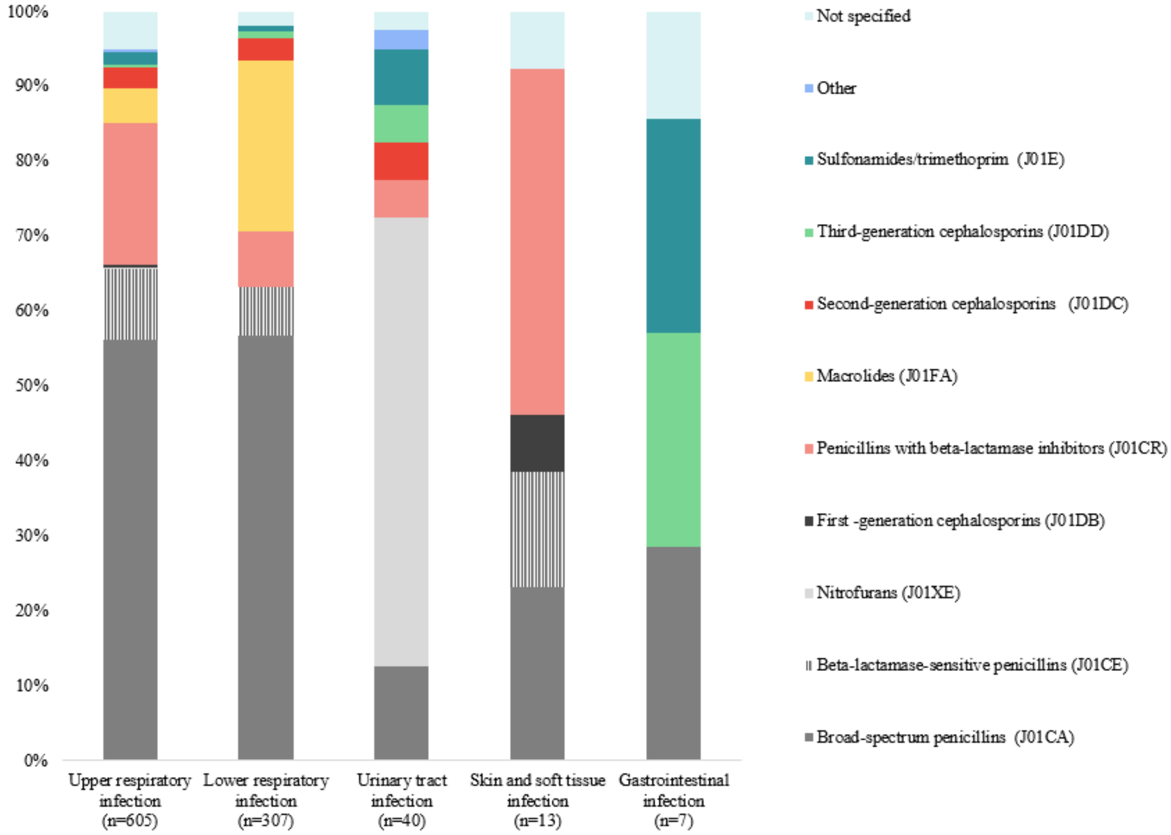

Figure 2.6 **Narrow- and broad-spectrum antibiotic prescribing according to infection location**

In the figure, narrow-spectrum antibiotics are indicated in shades of black and gray, while broad-spectrum antibiotics are shown in other colours. For 40 patients, antibiotic treatment was prescribed, but the specific antibiotic used was not reported

2.4 Patient- and GP-related predictors of antibiotic prescribing

To assess the association between various GP-related and patient- related factors and antibiotic prescribing, logistic regression analysis was performed. According to the results of the univariable analysis (Table 2.4), three patient-related factors showed a statistically significant increase in the odds of receiving an antibiotic prescription. Antibiotics were prescribed almost 20 % more frequently to girls compared with boys (OR 1.17 (95 % CI 1.00–1.36), $p = 0.045$). Antibiotic prescribing was more common with a longer duration of symptoms. When symptom duration reached 3 days, antibiotic prescribing increased by almost 90 % compared with 1 day (OR 1.88 (95 % CI 1.28–2.76), $p = 0.001$) and reached the highest level on day 4 (OR 2.24 (95 % CI 1.50–3.34), $p < 0.001$). Compared with upper respiratory tract infections, antibiotics were prescribed 3 times more often for lower respiratory tract infections (OR 3.1 (95 % CI 2.6–3.7), $p < 0.001$), 14 times more often for urinary tract infections (OR 14.3 (95 % CI 6.9–29.6), $p < 0.001$), and 6 times more often for skin and soft tissue infections (OR 6.0 (95 % CI 2.4–15.0), $p < 0.001$).

Among GP-related factors, a statistically significant association was observed for GP age. GPs aged 41–50 years had a two-fold higher likelihood of prescribing antibiotics compared with younger GPs aged 30–40 years (OR 2.05 (95 % CI 1.63–2.59), $p < 0.001$), while antibiotic prescribing increased by nearly 40 % among GPs aged over 61 years (OR 1.38 (95 % CI 1.09–1.73), $p = 0.006$). GPs with more than 21 years of work experience had 40 % higher antibiotic prescribing rates than those with less than 5 years of practice (OR 1.40 (95 % CI 1.08–1.80), $p = 0.01$), whereas GPs with 6–10 years of experience showed 60 % lower prescribing rates compared with those with under 5 years of experience (OR 0.40 (95 % CI 0.25–0.66), $p < 0.001$). Higher antibiotic prescribing was also observed in practices with fewer registered paediatric patients (<500 vs. >1001: OR 1.39 (95 % CI 1.10–1.77), $p = 0.007$; and 501–1000 vs. >1001: OR 1.50 (95 % CI 1.28–1.76), $p < 0.001$).

In the second stage, multivariable analysis was performed, adjusting for all independent variables listed in Table 2.4. GP age and GP work experience were not included in the same model due to strong collinearity. Therefore, two separate models were developed, including either work experience or age. After adjustment for all factors, all previously identified patient-related factors remained significantly associated with more frequent antibiotic prescribing, except for symptom duration of 5 days. Among GP-related variables, the 41–50-year age group and a lower number of registered paediatric patients remained significant, while work experience became associated starting from 11 years.

In the third stage, a mixed-effects logistic regression model (generalized linear mixed model with binomial distribution) was used. In this model, the previously mentioned factors were included as fixed effects, while the GP practice identifier was included as a random effect. This approach allows for the possibility that observations within the same practice may be correlated, forming clusters. The results of the full model showed that individual GP prescribing behaviour was a statistically significant factor (random-effects variance = 0.79, $p < 0.001$), and nearly 20 % of the total variance in antibiotic prescribing could be attributed to differences between GP practices (variance partition coefficient was 19.3 %). Thus, patients within a single practice cannot be considered independent observations but instead form clusters in which patient experience is more similar than between clusters due to the GP's specific prescribing approach. Consequently, all subsequent regression models were constructed as mixed-effects models, incorporating the GP practice identifier as a second level random effect to account for clustering.

After adding the GP practice identifier to the model, several previously observed GP-related factors lost their statistical significance. A 75 % higher likelihood of receiving an antibiotic prescription was observed in practices with 501–1000 registered children (501–1000 vs. >1001: OR 1.75 (95 % CI 1.03–2.98), $p = 0.04$).

Table 2.4

Patient- and GP-related predictors of antibiotic prescribing

	Univariate logistic regression analysis			Multivariable logistic regression analysis			Mixed-effects logistic regression model		
Character-istics	**OR**	**95 % CI**	**p value**	**aOR***	**95 % CI**	**p value**	**aOR****	**95 % TI**	**p value**
Patient-related factors									
Age									
15–17 years	1.21	0.86–1.69	0.27	1.21	0.84–1.76	0.306	1.25	0.83–1.87	0.282
10–14 years	0.80	0.63–1.02	0.07	0.82	0.63–1.06	0.131	0.80	0.60–1.06	0.121
5–9 years	0.93	0.79–1.11	0.44	0.98	0.82–1.19	0.864	0.96	0.79–1.18	0.717
1 month–4 years	1	–	–	1	–	–	1	–	–
Sex									
Boys	1	–	–	1	–	–	1	–	–
Girls	**1.17**	**1.00–1.36**	**0.045**	**1.19**	**1.01–1.39**	**0.039**	1.12	0.94–1.33	0.206
Duration of symptoms (days)									
1	1	–	–	1	–	–	1	–	–
2	1.48	1.00–2.18	0.05	1.33	0.88–2.03	0.18	1.14	0.74–1.77	0.552
3	**1.88**	**1.28–2.76**	**0.001**	**1.56**	**1.03–2.36**	**0.037**	1.33	0.86–2.06	0.201
4	**2.24**	**1.50–3.34**	**< 0.001**	**1.80**	**1.17–2.77**	**0.008**	**1.61**	**1.02–2.54**	**0.04**
5	**1.93**	**1.26–2.95**	**0.002**	1.46	0.92–2.32	0.107	1.36	0.83–2.13	0.217
Location of infection									
Upper RI	1	–	–	1	–	–	1	–	–
Lower RI	**3.1**	**2.6–3.7**	**< 0.001**	**2.86**	**2.37–3.48**	**< 0.001**	**2.49**	**2.01–3.08**	**< 0.001**
GI	**0.3**	**0.2–0.7**	**0.007**	**0.36**	**0.16–0.80**	**0.012**	**0.33**	**0.15–0.76**	**0.008**
UTI	**14.3**	**6.9–29.6**	**< 0.001**	**14.0**	**6.63–29.6**	**< 0.001**	**17.24**	**7.70–38.60**	**< 0.001**
Skin and soft tissue	**6.0**	**2.4–15.0**	**< 0.001**	**4.56**	**1.88–11.08**	**< 0.001**	**3.67**	**1.45–9.25**	**0.006**
Comorbidities									
Yes	1,1	0.9–1.5	0.36	1.04	0.78–1.39	0.797	0.88	0.64–1.22	0.449
No	1	–	–	1	–	–	1	–	–
Vaccination									
No	0.5	0.2–1.3	0.15	0.52	0.20–1.30	0.16	0.53	0.21–1.37	0.19
Partial	**0.7**	**0.5–1.0**	**0.039**	0.80	0.54–1.16	0.238	0.77	0.52–1.15	0.2
Full	1	–	–	1	–	–	1	–	–

Table 2.4 continued

	Univariate logistic regression analysis			**Multivariable logistic regression analysis**			**Mixed-effects logistic regression model**		
Characte-ristics	**OR**	**95 % CI**	**p value**	**aOR***	**95 % CI**	**p value**	**aOR****	**95 % TI**	**p value**
GP-related factors									
Age (years)									
30–40	1	–	–	1	–	–	1	–	–
41–50	**2.05**	**1.63–2.59**	**< 0.001**	**2.15**	**1.62–2.86**	**< 0.001**	1.91	0.89–4.13	0.099
51–60	1.09	0.87–1.37	0.47	1.07	0.83–1.39	0.599	1.23	0.62–2.43	0.562
61+	**1.38**	**1.09–1.73**	**0.006**	1.21	0.92–1.58	0.173	1.37	0.66–2.84	0.404
Sex									
Male	1	–	–	1	–	–	1	–	–
Female	0.76	0.47–1.23	0.27	0.83	0.48–1.41	0.487	1.30	0.28–5.93	0.737
Work experience (years)									
≤ 5	1	–	–	1	–	–	1	–	–
6–10	**0.40**	**0.25–0.66**	**< 0.001**	0.67	0.39–1.17	0.156	0.78	0.22–2.82	0.703
11–20	1.31	0.97–1.77	0.08	**1.68**	**1.18–2.40**	**0.004**	1.97	0.74–5.23	0.172
21+	**1.40**	**1.08–1.80**	**0.01**	**1.45**	**1.08–1.95**	**0.015**	1.65	0.74–3.66	0.219
Location of practice									
Rural	1.16	0.98–1.38	0.08	1.22	0.98–1.51	0.082	1.46	0.82–2.63	0.201
Regional cities	0.96	0.79–1.18	0.71	1.05	0.83–1.33	0.682	1.23	0.68–2.23	0.489
Capital of Latvia	1	–	–	1	–	–	1	–	–
Number of paediatric patients in practice									
≤ 500	**1.39**	**1.10–1.77**	**0.007**	**1.42**	**1.06–1.91**	**0.019**	1.37	0.56–3.32	0.492
501–1000	**1.50**	**1.28–1.76**	**< 0.001**	**1.54**	**1.27–1.86**	**< 0.001**	**1.75**	**1.03–2.98**	**0.04**
1001+	1	–	–	1	–	–	1	–	–
Expected time of laboratory results									
During W/D	1	–	–	1	–	–	1	–	–
Next W/D	0.97	0.84–1.13	0.71	1.10	0.93–1.31	0.271	1.12	0.69–1.82	0.979
2 W/Ds or longer	0.82	0.42–1.58	0.54	0.99	0.49–1.99	0.975	0.98	0.14–6.85	0.653

OR – unadjusted odds ratio from the univariate logistic regression model.
aOR* – odds ratio adjusted for all factors shown in the table, except physician age, from the multivariable logistic regression model.
aOR** – odds ratio adjusted for all factors shown in the table, except physician age, from the multivariable mixed-effects logistic regression model, in which physician practice is included as a random-effect variable representing the clustering of observations.
physician age is adjusted for all factors shown in the table except years of work experience.
RI – respiratory infections; GI – gastrointestinal infections; UTI – urinary tract infections.

2.5 Effects of interventions on antibiotic prescribing practices

Changes in antibiotic prescribing practices were described using three parameters across the study groups:

- the proportion of children who were prescribed antibiotics;
- the proportion broad-spectrum antibacterial agents;
- the proportion delayed antibiotic prescriptions.

2.5.1 Antibiotic prescribing in study groups

When comparing the study groups, the lowest rate of antibiotic prescribing was observed in the long-term educational group (24.9 % vs. 32.4 % in the usual care group (p = 0.001) and vs. 29.2 % in the combined intervention group (p = 0.03). No statistically significant difference was observed between the combined intervention group and the usual care group (see Figure 2.7).

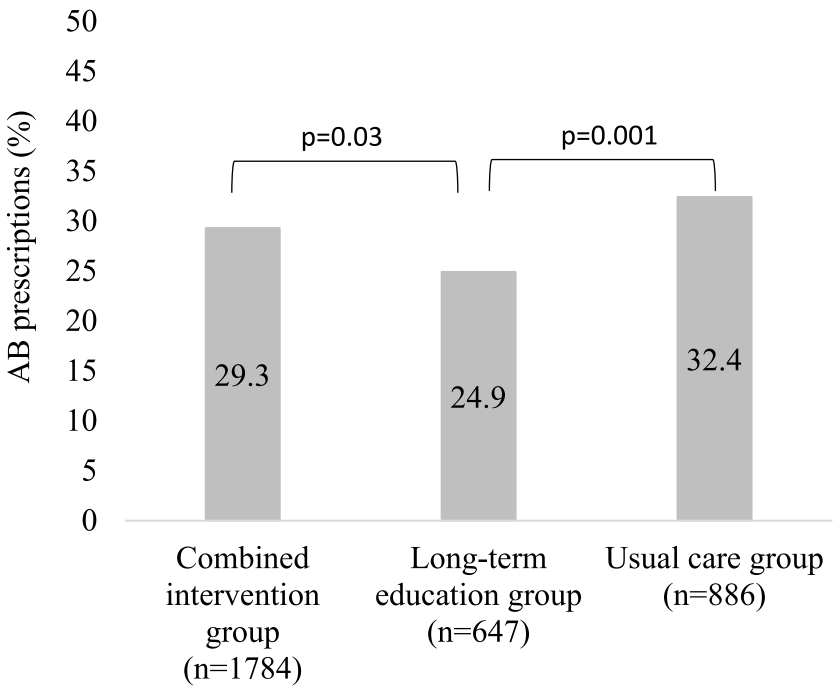

Figure 2.7 **Antibiotic prescribing in study groups**

AB – antibiotics

After adjusting for all independent patient- and GP-related factors (described in Table 2.4), the long-term education group showed a 30 % lower likelihood of antibiotic prescribing compared with the usual care group (aOR 0.68 (95 % CI 0.52–0.89), p = 0.004). However, when accounting for the clustering effect of GPs practices, the statistically significant differences between the long-term education group and the combined intervention and usual care groups disappeared (Table 2.5).

Table 2.5

Effect of combined intervention and long-term education intervention on antibiotic prescribing

	Univariate logistic regression analysis			Multivariable logistic regression analysis			Mixed-effects logistic regression analysis		
Study group	**OR**	**95 % CI**	**p**	**aOR***	**95 %**	**p**	**aOR****	**95 % CI**	**p**
Combined	0.87	0.73–1.03	0.11	0.89	0.74–1.09	0.257	0.99	0.77–1.28	0.943
Long-term	**0.69**	**0.55–0.87**	**0.001**	**0.68**	**0.52–0.89**	**0.004**	0.83	0.58–1.19	0.314
Usual care	1	–	–	1	–	–	1	–	–

CI – confidence interval
OR – unadjusted odds ratio from the univariate logistic regression model
aOR* – odds ratio adjusted for all independent variables – patient-related factors (age, sex, duration of symptoms, infection site, comorbidities, vaccination) and physician-related factors (age, sex, years of experience, practice location, proportion of paediatric patients in the practice, turnaround time for laboratory test results) – from the multivariable logistic regression model
aOR** – odds ratio adjusted for all independent variables – patient-related factors (age, sex, duration of symptoms, infection site, comorbidities, vaccination) and physician-related factors (age, sex, years of experience, practice location, proportion of paediatric patients in the practice, expected time for laboratory test results) – from the multivariable mixed-effects logistic regression model with physician practice included as a random effect

2.5.2 Delayed antibiotic prescriptions in study groups

Differences in the use of delayed prescriptions across the study groups are shown in Figure 2.8. Significantly fewer delayed prescriptions were used in the usual care group – 14.3 % of all prescriptions (vs. 22.9 % in the combined intervention group (p < 0.001) and vs. 22.4 % in the long-term education group (p = 0.03)). No statistically significant differences were observed between the combined intervention group and the long-term education group.

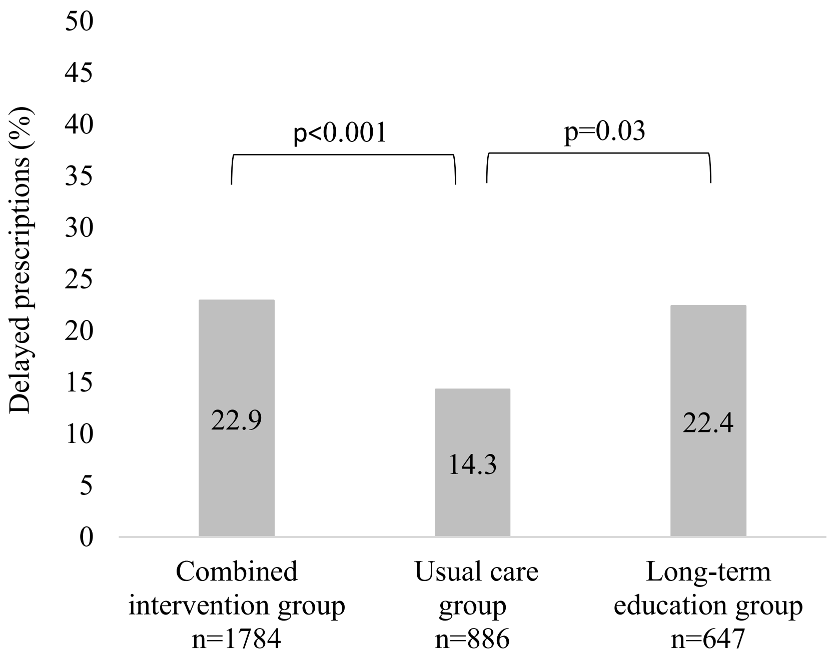

Figure 2.8 **Delayed antibiotic prescriptions in study groups**

However, in both the univariate and multivariable mixed-effects logistic regression models, after including the GPs practice identifier as a variable representing clusters, the differences in delayed prescriptions between study groups were no longer statistically significant (Table 2.6), although the overall direction of associations remained similar: in both intervention groups, the odds of using delayed prescriptions were higher compared with the usual care group.

In both the univariate and multivariable models, a statistically significant association with delayed prescription issuance was observed for infection site: in cases of urinary tract infections compared with upper respiratory tract infections, GP were 80 % less likely to use a delayed prescription (aOR 0.20 (95 % CI 0.04–0.94)).

Table 2.6

Effect of combined intervention and long-term education intervention on delayed antibiotic prescriptions

	Univariate mixed-effects logistic regression analysis			Multivariable mixed-effects logistic regression analysis		
Study group	**OR**	**95 % CI**	**p**	**aOR**	**95 % CI**	**p**
Combined intervention	1.40	0.84–2.35	0.202	1.34	0.77–2.32	0.305
Long-term education	1.22	0.61–2.43	0.578	1.25	0.58–2.67	0.572
Usual care	1	–	–	1	–	–

Results of mixed-effects logistic regression models, in which physician practice was included as a random-effect variable representing observation clusters:
OR – unadjusted odds ratio
aOR – odds ratio adjusted for all independent variables – patient-related factors (age, sex, duration of symptoms, infection site, comorbidities, vaccination) and GP-related factors (age, sex, years of experience, practice location, proportion of paediatric patients in the practice, expected time for laboratory test results)
CI – confidence interval

2.5.3 Broad-spectrum antibiotic prescribing in study groups

The study analysed the proportion of all prescribed antibacterial agents that were broad-spectrum (the classification of broad- and narrow-spectrum antibacterial agents is described in Section 2.3.3.). In the combined intervention group, 37.1 % of patients (n = 185) were prescribed broad-spectrum antibiotics, compared with 28.8 % (n = 45) in the long-term education group and 31.4 % (n = 89) in the usual care group. However, no statistically significant differences were observed between the groups (p = 0.12) (Figure 2.9).

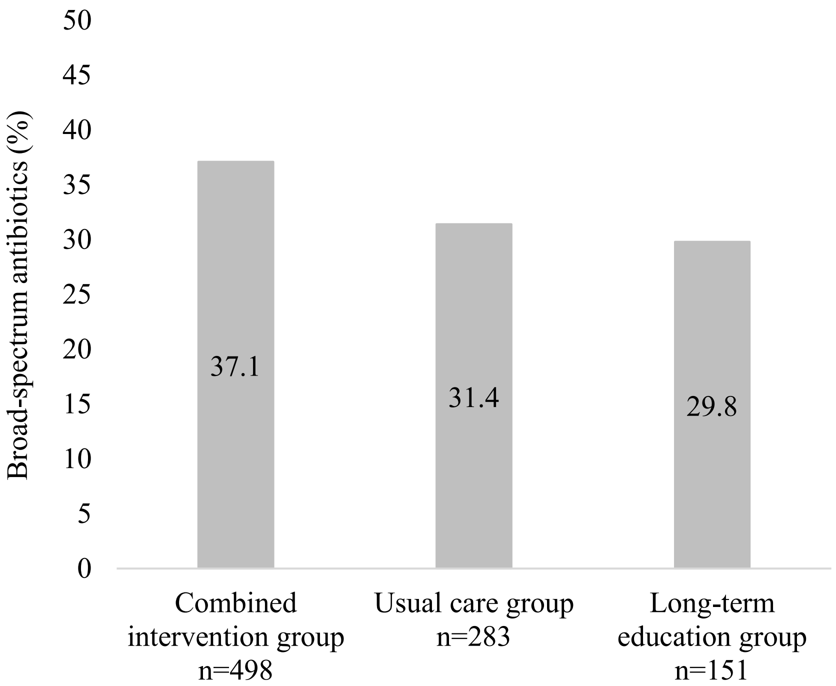

Figure 2.9 **Broad-spectrum antibiotic prescribing in study groups**

As expected, no association was observed between the prescribing of broad-spectrum antibiotics and study interventions in either the univariate or multivariable mixed-effects logistic regression models (Table 2.7). However, these models confirmed associations between broad-spectrum antibiotic prescribing and several other factors.

According to the univariate analysis, broad-spectrum antibiotics were more frequently prescribed with increasing patient age. Compared with children aged 1 month to 4 years, broad-spectrum antibiotics were prescribed approximately 50 % more often to children aged 5–9 years (OR 1.53 (95 % CI 1.09–2.16), $p = 0.015$), nearly twice as often to children aged 10–14 years (OR 1.95 (95 % CI 1.20–3.18), $p = 0.007$), and 2.3 times more often in the 15–17-year age group (OR 2.34 (95 % CI 1.27–4.34), $p = 0.007$).

A significant association was also observed with infection location. Compared with upper respiratory tract infections, children with skin, soft tissue, bone, and joint infections were almost four times more likely to be prescribed broad-spectrum antibiotics (OR 3.75 (95 % CI 1.10–12.82), $p = 0.035$), and in cases of lower respiratory tract infections, the likelihood was increased by 66 % (OR 1.66 (95 % CI 1.19–2.31), $p = 0.003$).

After adjusting for all independent variables, the above associations remained. Additionally, GPs with more than 21 years of experience prescribed broad-spectrum antibiotics nearly three times more often than those with less than 5 years of practice (aOR 2.96 (95 % CI 1.02–8.59), $p = 0.046$), while GPs practicing in rural areas prescribed them less frequently compared with GPs in Riga (aOR 0.42 (95 % CI 0.20–0.87), $p = 0.021$).

Table 2.7

Effect of combined intervention and long-term education intervention on broad-spectrum antibiotic prescriptions

	Univariate mixed-effects logistic regression analysis			Multivariable mixed-effects logistic regression analysis		
Study group	**OR**	**95 % CI**	**p**	**aOR**	**95 % CI**	**p**
Combined intervention	1.14	0.76–1.73	0.525	1.01	0.65–1.58	0.955
Long-term education	0.86	0.48–1.53	0.603	0.83	0.44–1.57	0.567
Usual care	1	–	–	1	–	–

Results of mixed-effects logistic regression models, in which physician practice was included as a random-effect variable representing observation clusters:
OR – unadjusted odds ratio
aOR – odds ratio adjusted for all independent variables – patient-related factors (age, sex, duration of symptoms, infection site, comorbidities, vaccination) and GP-related factors (age, sex, years of experience, practice location, proportion of paediatric patients in the practice, expected time for laboratory test results)
CI – confidence interval

2.6 Diagnostic practices prior to antibiotic prescribing and the impact of combined intervention and long-term education intervention

Overall, 52.5 % (n = 1.742) of study patients underwent at least one diagnostic test prior antibiotic prescribing (CRP POCT or laboratory CRP concentration, full blood count, urinalysis, AGBHS, rapid influenza test, chest X-ray), while 47.5 % (n = 1.575) did not undergo any testing. Among these patients, for 39.1 % (n = 1298) GPs considered diagnostic testing unnecessary, and for 8.3 % (n = 275), according to the GPs, the test would have been useful, but it was unavailable at the time of consultation.

The most frequently used diagnostic test was CRP test, either in the laboratory or as a POCT (42.5 %, n = 1409). Other tests were performed considerably less frequently (Table 2.8).

Table 2.8

Diagnostic tests performed in study patients

Diagnostic test	N	%
CRP	1409	42,5
GABHS	220	6,6
Full blood count	186	5,6
Urinalysis	157	4,7
Rapid influenza test	122	3,7
X-ray	99	3,0

CRP – C reactive protein
GABHS – Group A β haemolytic streptococcus test

To assess the association of various GP- and patient-related factors with the ordering of diagnostic tests, univariate and multivariable mixed-effects logistic regression models were used (Table 2.9). Considering the observed differences in antibiotic prescribing between GP practices, the GP practice identifier was included in the regression model as a random effect to account for clustering.

According to the univariate analysis, several factors were significantly associated with diagnostic testing. Tests were more frequently ordered with increasing patient age. Compared with children aged 1 month to 4 years, tests were ordered 30 % more often for children aged 5–9 years (OR 1.3 (95 % CI 1.1–1.5), p = 0.003), 50 % more often for children aged 10–14 years (OR 1.5 (95 % CI 1.2–2.0), p = 0.001), and nearly three times more often for patients aged 15–17 years (OR 2.9 (95 % CI 1.9–4.3), p < 0.001).

Diagnostic testing was also more frequent with longer symptom duration. As symptom duration increased from 2 to 5 days, the odds of ordering diagnostic tests increased from OR 2.3 (95 % CI 1.6–3.5) to OR 5.0 (95 % CI 3.2–7.8), compared with symptoms lasting 1 day. Tests were ordered eight times more often for patients with urinary tract infections than for those with upper respiratory tract infections (OR 8.0 (95 % CI 3.0–21.3), p < 0.001), and 40 % more often for patients with lower respiratory tract infections (OR 1.4 (95 % CI 1.1–1.8), p = 0.002).

Among GP-related factors, the only factor having a statistically significant association with diagnostic testing was the study intervention. In the univariate analysis, belonging to the combined intervention group, where physicians had access to CRP POCT, was associated with significantly more frequent testing (OR 11.5 (95 % CI 8.5–15.8), p < 0.001 vs. the control group), whereas in the long-term education group, where CRP POCT was no longer available, testing decreased by 40 % compared with the usual care group (OR 0.6 (95 % CI 0.4–0.9), p = 0.008).

After adjustment for all independent variables, all factors remained statistically significant, except for patient age groups 5–9 and 10–14 years. Importantly, in the multivariable analysis, after adjusting for all other factors, the association between study interventions and diagnostic test ordering remained significant.

Table 2.9

Patient- and GP-related predictors of diagnostic test usage

	Univariate mixed-effects logistic regression analysis			**Multivariable mixed-effects logistic regression analysis**		
Characteristics	**OR**	**95 % CI**	**p**	**aOR**	**95 % CI**	**p**
Patient-related factors						
Age						
15–17 years	**2.9**	**1.9–4.3**	**< 0.001**	**2.2**	**1.4–3.7**	**0.002**
10–14 years	**1.5**	**1.2–2.0**	**0.001**	1.3	1.0–1.8	0.080
5–9 years	**1.3**	**1.1–1.5**	**0.003**	1.2	1.0–1.5	0.131
1 months–4 years	1	–	–	1	–	–
Sex						
Girls	1.0	0.8–1.1	0.655	0.9	0.7–1.0	0.095
Boys	1	–	–	1	–	–

Table 2.9 continued

	Univariate mixed-effects logistic regression analysis			Multivariable mixed-effects logistic regression analysis		
Characteristics	**OR**	**95 % CI**	**p**	**aOR**	**95 % CI**	**p**
Patient-related factors						
Duration of symptoms (days)						
1	1	–	–	1	–	–
2	**2.3**	**1.6–3.5**	**< 0.001**	**1.7**	**1.0–2.6**	**0.032**
3	**3.1**	**2.1–4.7**	**< 0.001**	**2.2**	**1.4–3.4**	**0.001**
4	**4.2**	**2.8–6.4**	**< 0.001**	**2.9**	**1.8–4.7**	**< 0.001**
5	**5.0**	**3.2–7.8**	**< 0.001**	**2.6**	**1.5–4.5**	**< 0.001**
Location of infection						
Upper RI	1	–	–	1	–	–
Lower RI	**1.4**	**1.1–1.8**	**0.002**	**1.4**	**1.1–1.9**	**0.01**
GI infections	1.5	0.9–2.6	0.147	1.8	0.9–3.5	0.101
UTI	**8.0**	**3.0–21.3**	**< 0.001**	**28.2**	**9.0–87.7**	**< 0.001**
SSBJ	0.4	0.2–1.2	0.099	0.8	0.3–2.6	0.751
Comorbidities						
Yes	0.9	0.7–1.2	0.374	0.9	0.6–1.3	0.532
No	1	–	–	1	–	–
Vaccination						
Complete	1	–	–	1	–	–
No	0.7	0.5–1.1	0.098	0.8	0.5–1.20	0.266
Incomplete	0.9	0.4–2.0	0.792	1.2	0.4–3.5	0.729
GP-related factors						
Age (years)						
30–40	1	–	–	1	–	–
41–50	1.6	0.5–4.8	0.421	1.1	0.3–4.2	0.897
51–60	1.5	0.6–4.2	0.418	1.0	0.3–3.1	0.943
61+	2.5	0.9–7.5	0.091	2.0	0.6–7.0	0.295
Work experience (years)						
≤ 5	1	–	–	1	–	–
6–10	0.4	0.1–2.1	0.256	0.4	0.0–3.5	0.402
11–20	0.5	0.1–2.2	0.383	0.3	0.1–1.8	0.203
21+	1.3	0.4–3.9	0.689	0.8	0.2–3.0	0.693
Location of practice						
Rural	1.1	0.5–2.4	0.877	1.2	0.4–3.4	0.715
Regional cities	1.5	0.6–3.6	0.426	1.4	0.5–4.1	0.532
Capital of Latvia	1	–	–	1	–	–
Number of paediatric patients in practice						
≤ 500	2.1	0.6–7.9	0.246	4.6	1.0–21.7	0.057
501–1000	1.1	0.5–2.4	0.771	1.1	0.4–2.9	0.808
1001+	1	–	–	1	–	–

Table 2.9 continued

	Univariate mixed-effects logistic regression analysis			Multivariable mixed-effects logistic regression analysis		
Characteristics	**OR**	**95 % CI**	**p**	**aOR**	**95 % CI**	**p**
Study group						
Combined intervention	**11.5**	**8.5–15.8**	**< 0.001**	**11.1**	**8.0–15.3**	**< 0.001**
Long-term education	**0.6**	**0.4–0.9**	**0.008**	**0.5**	**0.3–0.8**	**0.006**
Usual care	1	–	–	1	–	–

Results of mixed-effects logistic regression models, in which physician practice was included as a random-effect variable representing observation clusters:
OR – unadjusted odds ratio
aOR – odds ratio adjusted for all other factors shown in the table, except GP years of experience; GP age – adjusted for all factors shown in the table, except years of experience
GI – gastrointestinal infections
SSBJ – skin, soft tissue, bone, and joint infections
UCI – urinary tract infections
RI – respiratory infections

Overall, the diagnostic testing level was highly variable among the three study groups (Figure 2.10). Approximately one-third of patients underwent any diagnostic test in the usual care and long-term education group, whereas 72.6 % were tested in the combined intervention group. In the study groups without access to CRP POCT (long-term education and usual care group), GPs were more likely to consider testing unnecessary (24.1 % in the combined intervention group vs. 53.7 % in the usual care group and 60.7 % in the long-term education group, p < 0.001).

In addition, 15.0 % of cases in the usual care group and 12.8 % of cases in the long-term education group were deemed by GPs to warrant testing but were unable to undergo testing before antibiotic prescribing due to the time delay of laboratory results or lack of POCT in the practice, compared with only 3.3 % in the combined intervention group (p < 0.001).

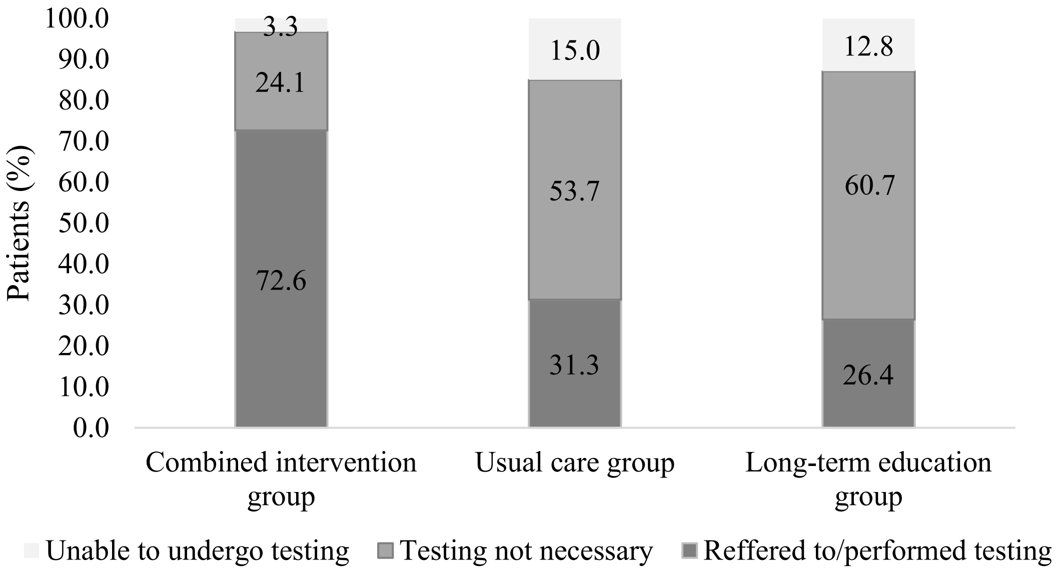

Figure 2.10 **Comparison of availability and use of diagnostic tests in the three study groups**

The effect of the study intervention varied according to the urbanicity level of GP practice and the expected time of laboratory results (Table 2.10). The effect of the interventions on diagnostic testing was analysed separately for each subgroup (stratified analysis).

In GPs practices in rural areas and regional cities, belonging to the combined intervention group with access to CRP POCT increased the likelihood of diagnostic testing more than 30-fold compared with the usual care group (aOR 37.6 (95 % CI 17.9–79.0), p < 0.001 and aOR 31.6 (95 % CI 13.8–72.1), p < 0.001, respectively), whereas in practices in Riga, testing increased only fivefold (aOR 5.0 (95 % CI 3.3–7.5), p < 0.001). Similar results were observed when comparing groups regarding the expected time of laboratory results. When GPs could receive results within one working day, testing in the combined intervention group increased fivefold (aOR 5.6 (95 % CI 3.6–8.9), p < 0.001), but when results took more than one working day, testing increased 23-fold (aOR 23.2 (95 % CI 14.1–38.0), p < 0.001).

In the long-term education group, test ordering decreased by 90 % in rural practices compared with the usual care group (aOR 0.1 (95 % CI 0.0–0.4), p < 0.001) but increased threefold in practices in regional cities (aOR 3.1 (95 % CI 1.1–9.3), p = 0.041). Testing also decreased by 70 % in practices where laboratory results were available within one working day (aOR 0.3 (95 % CI 0.2–0.6), p < 0.001).

Table 2.10

Effect of combined intervention and long-term education intervention on diagnostic testing according to practice location and expected time of laboratory results

Characte-ristics	Combined intervention		Long-term education		Combined intervention		Long-term education	
	OR (95 % CI)	p	OR (95 % CI)	p	aOR (95 % CI)	p	aOR (95 % CI)	p
Expected time of laboratory results								
During working day	**5.5 (3.6–8.4)**	**< 0.001**	**0.3 (0.2–0.6)**	**< 0.001**	**5.6 (3.6–8.9)**	**< 0.001**	**0.3 (0.2–0.6)**	**< 0.001**
> 1 working day	**24.0 (15.1–38.4)**	**< 0.001**	0.8 (0.4–1.7)	0.594	**23.2 (14.1–38.0)**	**< 0.001**	0.7 (0.3–1.5)	0.385
Practice location								
Rural	**35.5 (17.4–72.3)**	**< 0.001**	**0.2 (0.1–0.6)**	**0.002**	**37.6 (17.9–79.0)**	**< 0.001**	**0.1 (0.0–0.4)**	**< 0.001**
Regional cities	**22.1 (10.6–45.7)**	**< 0.001**	**2.6 (1.0–6.7)**	**0.048**	**31.6 (13.8–72.1)**	**< 0.001**	**3.1 (1.1–9.3)**	**0.041**
Capital city	**5.4 (3.6–8.1)**	**< 0.001**	0.9 (0.5–1.5)	0.59	**5.0 (3.3–7.5)**	**< 0.001**	0.9 (0.5–1.6)	0.675

The data presented are results of logistic mixed effects models with GP practices as random effects. Results show the odds ratio of diagnostic testing in intervention groups (combined intervention and long-term education) versus the usual care group.
OR – odds ratio compared with the control group from the univariate mixed-effects logistic regression model, with GPs practice included as a random effect.
aOR – odds ratio adjusted for patient-related factors (age, sex, symptom duration, infection site, comorbidities, vaccination) and GP-related factors (years of experience, proportion of paediatric patients in the practice), compared with the control group, from the multivariable mixed-effects logistic regression model with GP practice included as a random effect.

Use of diagnostic tests also varied widely across different diagnoses in the study groups (Table 2.11). CRP testing was performed significantly more often for all diagnoses in the combined intervention group, except in patients with pneumonia, where no statistically significant differences were observed between the combined intervention, long-term education, and usual care groups. Overall, more than half of patients with respiratory tract infections in the combined intervention group had CRP measured.

For patients with pharyngotonsillitis, GABHS testing was relatively rare across all study groups, with the lowest testing frequency in the long-term education group (12.9 %). It was performed in 19.3 % of patients in the combined intervention group and 29.1 % in the usual care group ($p < 0.001$). CRP testing was relatively common in pharyngotonsillitis patients in the combined intervention group (70.6 %), whereas these patients were rarely referred for laboratory CRP measurement (18.6 % in the long-term education group and 5.0 % in the usual care group, $p < 0.001$).

For patients with pneumonia, X-ray were performed more frequently in the usual care group (56.0 %) compared with the combined intervention group (28.8 %) and the long-term education group (21.4 %, $p = 0.03$). Urinalysis was performed similarly across all study groups, but in the combined intervention group, CRP POCT was more frequently ordered for patients with urinary tract infections (70.0 %, n = 12 vs. 30.0 % in the usual care group and 15.8 % in the long-term education group, $p = 0.002$).

Table 2.11

Heatmap of diagnostic test usage (% of patients) prior to antibiotic prescribing according to diagnoses across the three study groups

Diagnostic tests	Diagnoses	Study group			Diagnoses	Study group		
		Combined intervention	Long-term education	Usual care		Combined intervention	Long-term education	Usual care
GABHS	Otitis (n = 223)	0.9	0	11.3	Pneumonia (n = 91)	0	0	0
CRP		52.6	6.7	9.7		69.2	21.4	44.0
FBC		0	6.7	4.8		3.8	28.6	32.0
Influenza test		1.7	0	3.2		9.6	0	8.0
X-ray		0	0	0		28.8	21.4	56.0
Urinalysis		1.7	0	6.5		5.8	14.3	8.0
GABHS	Pharyngotonsillitis (n = 737)	19.3	12.9	29.1	GI infection (n = 73)	0	0	0
CRP		70.6	18.6	5.0		75.6	38.5	5.3
FBC		2.3	15.7	5.0		7.3	23.1	5.3
Influenza test		1.5	0	8.5		2.4	0	0
X-ray		0	0.7	0		0	0	0
Urinalysis		2.3	5.7	3.0		12.2	30.8	31.6

Table 2.11 continued

Diagnostic tests	Diagnoses	Study group			Diagnoses	Study group		
		Combined intervention	Long-term education	Usual care		Combined intervention	Long-term education	Usual care
GABHS	Rhinosinusitis (n = 244)	3.6	1.1	5.4	UTI (n = 49)	0	0	10
CRP		55.4	5.3	2.7		70.0	15.8	30.0
FBC		1.8	2.1	2.7		0	21.1	10.0
Influenza test		0.9	0	8.1		0	0	10.0
X-ray		0.9	0	0		0	0	0
Urinalysis		4.5	0	5.4		45.0	78.9	80.0
GABHS	Common cold (n = 1342)	3.3	0	1.3	Skin and soft tissue infection (n = 20)	12.5	0	0
CRP		69.3	16.7	6.1		12.5	0	0
FBC		1.6	15.8	5.3		12.5	0	0
Influenza test		3.7	6.0	6.9		0	0	0
X-ray		1.7	2.3	0.5		0	0	0
Urinalysis		3.2	0.5	3.7		0	0	0
GABHS	Bronchitis (n = 534)	4.9	1.1	3.9	Bone and joint infection (n = 4)	0	100	0
CRP		79.3	16.0	14.2		50.0	0	100
FBC		2.8	14.9	11.6		0	0	100
Influenza test		3.2	0	3.9		0	0	0
X-ray		7.0	13.8	7.7		0	0	0
Urinalysis		4.6	2.1	8.4		0	0	0

The colour shades represent the frequency of testing (%) in ascending order – green, yellow, orange, and red. GABHS – Group A β haemolytic streptococcus; CRP = c reactive protein; FBC – full blood count; UTI – urinary tract infection; GI – gastrointestinal infection

2.7 Relationship between diagnostic testing and antibiotic prescribing

Antibiotic prescribing according to the performance and availability of diagnostic tests is shown in Figure 2.11. Almost half of patients (47.6 %) for which GPs deemed a diagnostic test(s) was necessary but unavailable at the time of consultation, received an antibiotic prescription. In contrast, a lower proportion of patients received an antibiotic prescription when a diagnostic test(s) was performed prior to making a decision (35.2 %). This was also the case when GPs thought diagnostic testing was not necessary (17.6 %). A statistically significant difference was observed between the groups ($p < 0.001$).

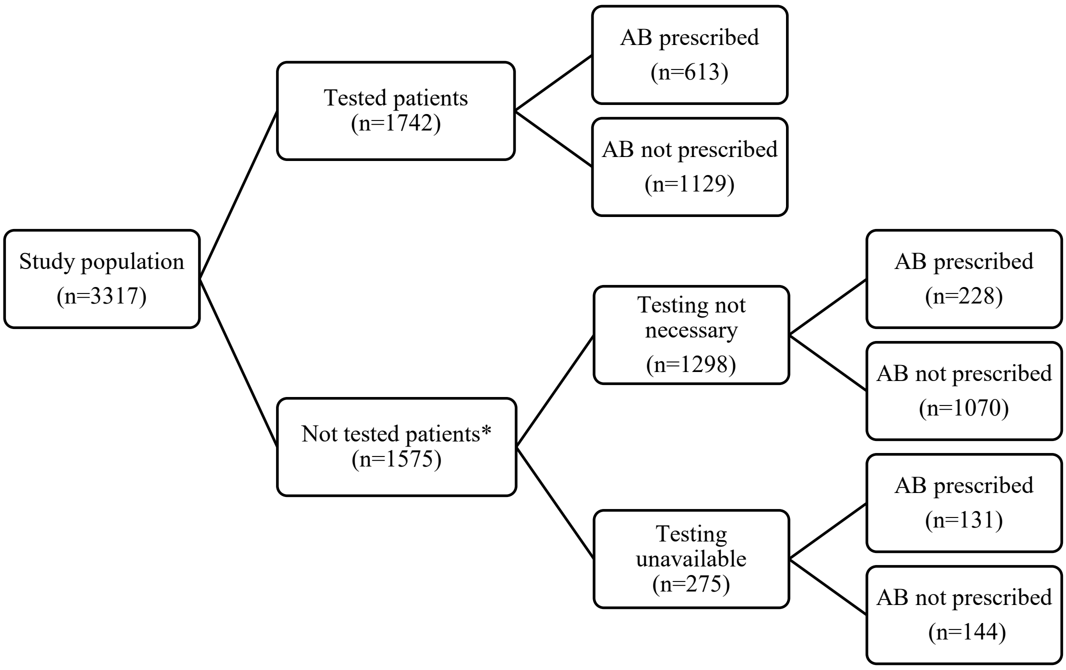

Figure 2.11 **Proportion of patients receiving an antibiotic prescription according to diagnostic testing**

*For 2 of the untested patients, it was not indicated whether the test was unnecessary or unavailable.
AB – antibiotics

2.8 CRP measurement and interpretation prior to antibiotic prescribing

Overall, CRP was measured for 1409 patients (42.5 %). The frequency of testing varied significantly between study groups. In the combined intervention group, where GPs had access to CRP POCT during the visit, CRP was measured in 1233 patients (69.1 %). In contrast, CRP was measured significantly less frequently in the long-term education group (14.8 %, n = 98) and in the usual care group (8.8 %, n = 78), where patients had to be referred to a laboratory for testing ($p < 0.001$).

For the majority of tested patients, CRP did not exceed 20.0 mg/L (78.3 %), while only about one-fifth of patients had CRP levels above 20.0 mg/L (21.7 %). The distribution of patients by CRP level is shown in Figure 2.12.

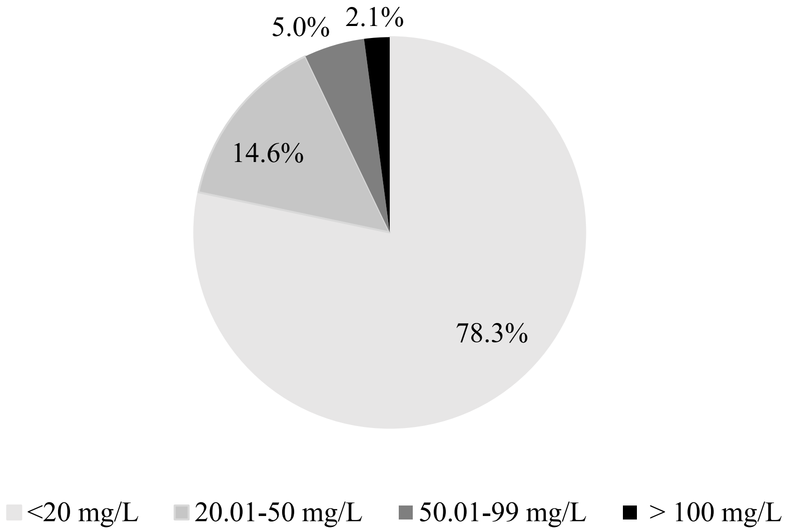

Figure 2.12 **CRP level for tested patients**

CRP levels in study patients, according to antibiotic prescribing, are visually presented in a boxplot (Figure 2.13). The median CRP level was significantly higher in patients who received antibiotics (24.0 mg/L, IQR 11.0–49.0) compared with patients who received a delayed prescription (8.6 mg/L, IQR 3.7–20.8) or did not receive antibiotics (2.9 mg/L, IQR 0.8–8.4), p < 0.001 across all groups.

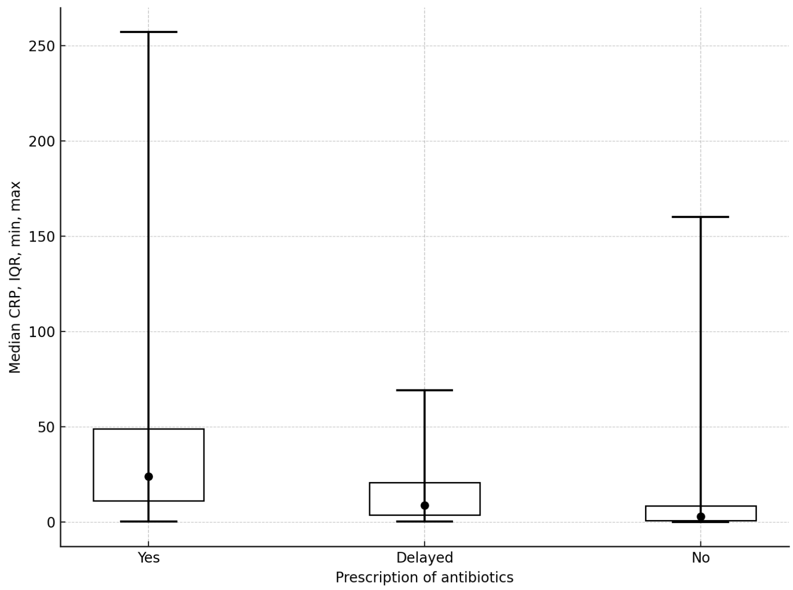

Figure 2.13 **Median CRP boxplot for patients with, without, and with a delayed antibiotic prescription**

Overall, the frequency of antibiotic prescribing increased with higher CRP levels across all diagnostic groups, except for pneumonia and urinary tract infections, where differences in antibiotic prescribing at different CRP levels were not statistically significant (p = 0.54 and p = 0.99, respectively). Figure 2.14 compares antibiotic prescribing across different diagnostic groups according to CRP levels.

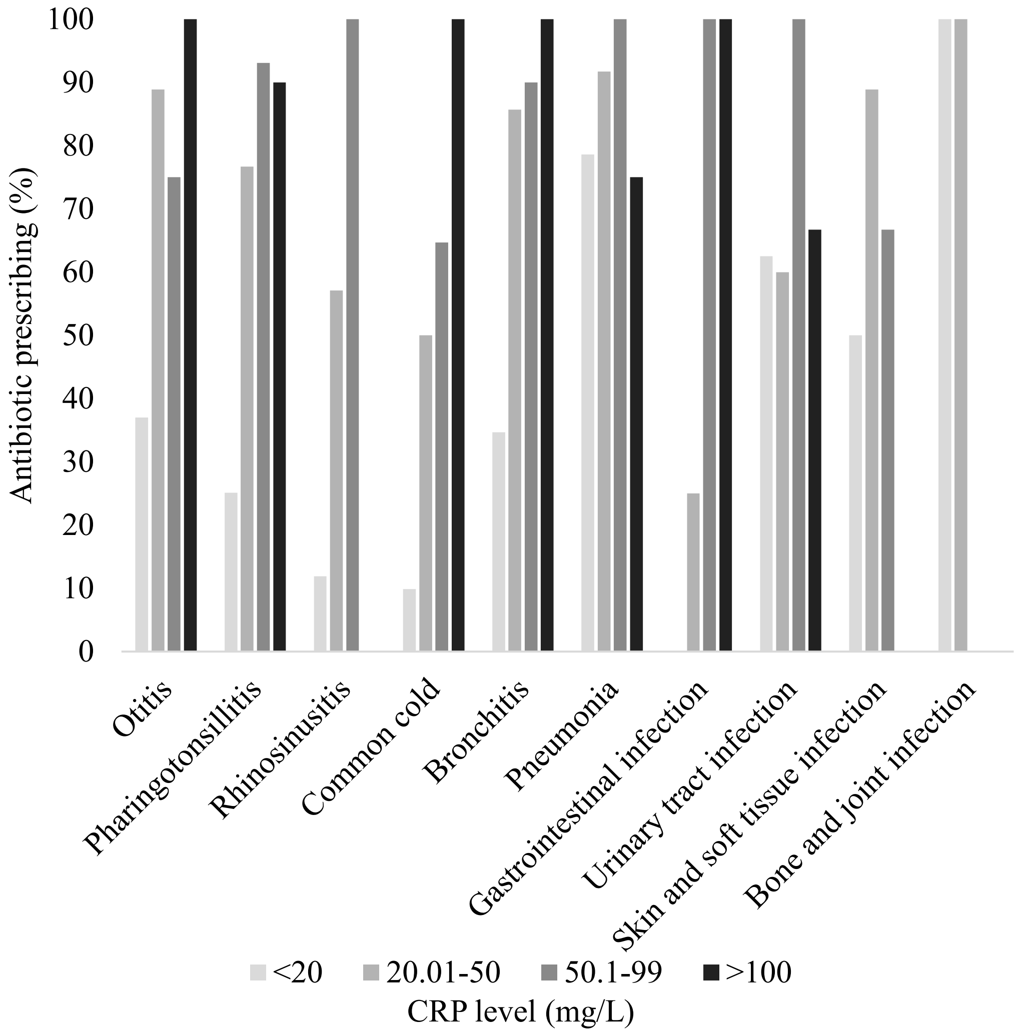

Figure 2.14 **Proportion of patients receiving an antibiotic prescription according to CRP level for different diagnoses**

Figure 2.15 shows antibiotic prescribing according to CRP levels across study groups. Overall, 26.7 % of patients without a measured CRP level were prescribed antibiotics. This was observed more frequently in the usual care group than in the combined intervention group (31.1 % vs. 24.3 %, $p = 0.007$) and the long-term education group (31.1 % vs. 22.9 %, $p < 0.001$). One in five patients (20.9 %) received antibiotics even when CRP levels did not exceed 20.0 mg/L, but this was less common in the combined intervention group compared with the usual care group (20.3 % vs. 35.4 %, $p = 0.012$).

Antibiotic prescribing increased with higher CRP levels: 69.4 % for CRP 20.1–50.0 mg/L, 85.9 % for CRP 50.1–99.9 mg/L, and 89.7 % for CRP >100 mg/L. No statistically significant differences between study groups were observed when CRP exceeded 20.0 mg/L. Patients with CRP >100 mg/L who did not receive antibiotics were referred to the hospital for further observation and treatment.

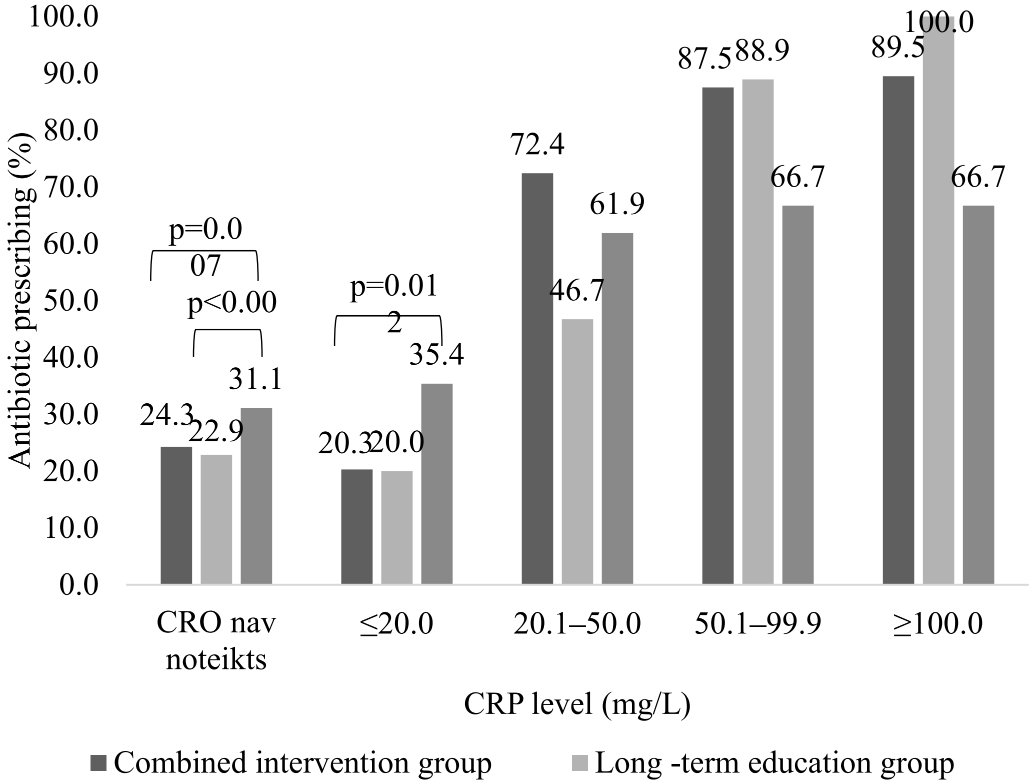

Figure 2.15 **Antibiotic prescribing at different CRP levels across study groups**

Conclusions

1. The overall antibiotic prescribing level for children with acute infections was low and consistent with data from other high-income countries. However, the findings highlight several potential areas for improvement, including avoiding antibiotic use during the initial days of illness or in cases of self-limiting viral infections, as well as reducing the prescription of broad-spectrum antibiotics.
2. Higher rates of antibiotic prescribing were associated with several patient-related factors (longer duration of symptoms, and infections of the lower respiratory tract, urinary tract, and skin and soft tissues) as well as GP-related factors (smaller number of paediatric patients registered in the practice). Moreover, individual GP prescribing habits represented a statistically significant factor, accounting for 20 % of the overall variability in antibiotic use.
3. The combination of CRP POCT and one-time GP education intervention as well as education intervention in long-term does not have a significant effect on overall antibiotic prescribing or the use of broad-spectrum antibiotics. Although both intervention groups prescribed delayed prescriptions more frequently compared with the usual care group, when GP practices were included in the model as the second-level variable indicating clusters, any differences in antibiotic prescription between the intervention groups became non-significant.
4. The study identified several factors associated with increased use of broad-spectrum antibiotics. These antibiotics were more frequently prescribed to older children and to patients with skin and soft tissue or lower respiratory tract infections. In addition, general practitioners with longer professional experience were more likely to prescribe broad-spectrum antibiotics.
5. The study revealed that decisions to prescribe antibiotics were predominantly based on clinical signs rather than on objective diagnostic test results, if tests were not available as point-of-care diagnostics. CRP POCT availability and GP education significantly increased diagnostic testing prior to antibiotic prescribing for all acute infections. A more pronounced increase in diagnostic testing was observed in practices located in rural areas and regional cities, as well as, in practices with a poorer accessibility to laboratories where minimal testing has been performed before the study.
6. CRP measurement was the most frequently used test for children with acute infections before antibiotic prescribing, particularly if GPs had access to it as a POCT. However, in the absence of clearly defined indications, POCT use becomes unnecessarily widespread, and low CRP concentrations (<20 mg/L) do not always convince GPs to withhold antibiotics.
7. Combined intervention and education intervention in long-term reduced antibiotic prescribing for patients without CRP testing and for patients with low CRP levels (<20 mg/L).

Proposals

1. The use of POCT, when combined with clinical assessment, has the potential to reduce inappropriate antibiotic prescribing. Based on the experience gained during the study, several general practitioners have continued to use CRP POCT in their daily practice, and since 2023 this test has also been implemented in the Emergency Department of the Children's Clinical University Hospital. However, ensuring test availability alone is insufficient to enhance its practical utility. Further education of general practitioners on the rational use of testing, as well as the development of evidence-based criteria for interpreting CRP POCT results, is essential to guide appropriate antibiotic prescribing
2. Education of physicians on rational antibiotic use is a key component in addressing antimicrobial resistance; however, passive educational activities alone do not provide sufficient effectiveness. These should be complemented by regular monitoring of antibiotic prescribing practices and structured feedback to clinicians to support improvements in clinical practice. Moreover, educational interventions should target not only healthcare professionals but also patients and their caregivers, thereby establishing a comprehensive approach to optimizing antibiotic use and strengthening public awareness of antimicrobial resistance.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. Likopa, Z., Kivite-Urtane, A. and Pavare, J. 2021. Latvian Primary Care Management of Children with Acute Infections: Antibiotic-Prescribing Habits and Diagnostic Process Prior to Treatment. *Medicina* (B. Aires)., 57. doi: 10.3390/MEDICINA57080831.
2. Likopa, Z., Kivite-Urtane, A., Silina, V. and Pavare, J. 2022. Impact of educational training and C-reactive protein point-of-care testing on antibiotic prescribing in rural and urban family physician practices in Latvia: a randomised controlled intervention study. *BMC Pediatr.*, 22, 1–10. doi: 10.1186/S12887-022-03608-4/TABLES/5.
3. Likopa, Z., Kivite-Urtane, A., Strele, I. and Pavare, J. 2024. Effect of Combination of Point-of-Care C-Reactive Protein Testing and General Practitioner Education and Long-Term Effect of Education on Reducing Antibiotic Prescribing for Children Presenting with Acute Infections in General Practice in Latvia: A Randomized Controlled Intervention Study. Antibiot. 2024, 13, 867. doi: 10.3390/ANTIBIOTICS13090867.
4. Likopa, Z., Kivite-Urtane, A., Strele, I. and Pavare, J. 2025. Improved diagnostic management of children with acute infectionsfollowing the introduction of point-of-care C-reactive proteintesting and general practitioner education in Latvia: a post hocanalyses of a randomised controlled intervention study. Scandinavian Journal of Primary Health Care. 2025 Oct 29. Epub 2025 Oct 29. doi: 10.1080/02813432.2025.2571927

Reports and theses at international congresses and conferences:

1. Likopa, Z., Kovalovs, S., Vasilevska, L., Reimane, E., Miluna, L., Pavare, J. 2021. Immediate antibiotic prescribing habits for acutely ill children in primary care. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences "Knowledge for Use in Practice": Abstracts, 24.–26.03.2021 (oral presentation).
2. Likopa, Z., Kivite-Urtane, A., Pavare, J. 2022. Impact of two interventions (C reactive protein point-of-care testing and education) on antibiotic prescribing for children with acute infections in primary care in Latvia. 40th Annual Meeting of the European Society of Paediatric Infectious: Abstracts, 09–13.05.2022 (poster presentation).
3. Likopa, Z., Kivite-Urtane, A., Pavare, J. 2022. Effect of C reactive protein point-of-care testing and family physician education on antibiotic prescribing for children with acute respiratory illnesses in primary care in Latvia. The 9th Congress of the European Academy of Paediatric Societies,7.–11.10.2022, Frontiers Event Abstracts 2022 (poster presentation)
4. Likopa, Z., Kivite-Urtane, A., Pavare, J. 2023. Patient- and family physician-related predictors of antibiotic prescribing and point-of-care and laboratory C reactive protein testing before decision making in rural and urban family physician practices in Latvia, 2023, Volume 59 Supplement 2 Medicina Abstracts of the International Scientific Conferences on Medicine & Public Health Research Week 2023 Rīga Stradiņš University, p. 73 (poster presentation)
5. Likopa, Z., Pavare, J. 2025. Effect of combination of point-of-care C-reactive protein testing and educational training on antibiotic prescribing and diagnostic habits for children presenting with acute infections in general practice. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences "Knowledge for Use in Practice": Abstracts, 24.–28.03.2025 (oral presentation)
6. Likopa, Z., Kivite-Urtane, A., Pavare, J. 2025. Use of C reactive protein point-of-care test and rapid antigen detection test for group A streptococci for children with pharyngotonsillitis in primary care in Latvia. 43th Annual Meeting of the European Society of Paediatric Infectious: Abstracts, 26.–30.05.2025 (poster presentation).

References

1. Reingold, S.M., Grossman, Z., Hadjipanayis, A., Del Torso, S., Valiulis, A., Dembinski, L. and Ashkenazi, S. 2023. Pediatric antibiotic stewardship programs in Europe: a pilot survey among delegates of The European Academy of Pediatrics. *Front. Pediatr.*, 11, 1–5. doi: 10.3389/fped. 2023.1157542.
2. Murray, C.J., Ikuta, K.S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., *et al.* 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*, 399, 629–655. doi: 10.1016/S0140-6736(21)02724-0/GLOBAL_BURDEN_OF_BACTERIAL_ANTIMICROBIAL_RESISTANCE_IN_2019_A_SYSTEMATIC_ANALYSIS.PDF.
3. Collaborators, A.R. 2021. Articles Global burden of bacterial antimicrobial resistance 1990 – 2021 : a systematic analysis with forecasts to 2050. 10.1016/S0140-6736(24)01867-1. doi: 10.1016/S0140-6736(24)01867-1.
4. Llor, C. 2025. Expert Review of Respiratory Medicine C-reactive protein point-of-care testing to guide antibiotic prescribing for respiratory tract infections. *Expert Rev. Respir. Med.*, 00, 1–15. doi: 10.1080/17476348.2025.2510378.
5. Schrier, L., Hadjipanayis, A., del Torso, S., Stiris, T., Emonts, M. and Dornbusch, H.J. 2018. European Antibiotic Awareness Day 2017: training the next generation of health care professionals in antibiotic stewardship. *Eur. J. Pediatr.*, 177, 279–283. doi: 10.1007/s00431-017-3055-0.
6. Boucher, H.W., Talbot, G.H., Benjamin, D.K., Bradley, J., Guidos, R.J., Jones, R.N., Murray, B.E., Bonomo, R.A. and Gilbert, D. 2013. 10 × ’20 progress – Development of new drugs active against gram-negative bacilli: An update from the infectious diseases society of America. *Clin. Infect. Dis.*, 56, 1685–1694. doi: 10.1093/cid/cit152.
7. Avent, M.L., Cosgrove, S.E., Price-Haywood, E.G. and Van Driel, M.L. 2020. Antimicrobial stewardship in the primary care setting: From dream to reality? *BMC Fam. Pract.*, 21, 1–9. doi: 10.1186/s12875-020-01191-0.
8. 8. King, L.M., Fleming-Dutra, K.E. and Hicks, L.A. 2018. Advances in optimizing the prescription of antibiotics in outpatient settings. *BMJ*, 363, k3047. doi: 10.1136/bmj.k3047.
9. Menting, S.G.P., Redican, E., Murphy, J. and Bucholc, M. 2023. Primary Care Antibiotic Prescribing and Infection-Related Hospitalisation. *Antibiotics*, 12. doi: 10.3390/ANTIBIOTICS 12121685.
10. Taylor, M.G. and Palazzi, D.L. 2022. Antimicrobial Stewardship in the Pediatric Primary Care Setting. *Pediatr. Ann.*, 51, e196–e201. doi: 10.3928/19382359-20220315-01.
11. McDonagh, M.S., Peterson, K., Winthrop, K., Cantor, A., Lazur, B.H. and Buckley, D.I. 2018. Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review. *J. Int. Med. Res.*, 46, 3337–3357. doi: 10.1177/0300 060518782519.
12. A, P., A, B., R, A., L, B., J, H. and P, D. 2015. Use of antibiotics in children: a Danish nationwide drug utilization study. *Pediatr. Infect. Dis. J.*, 34, e16–e22. doi: 10.1097/INF.0000000000000519.
13. Jensen, J.N., Bjerrum, L., Boel, J., Jarløv, J.O. and Arpi, M. 2016. Parents’ socioeconomic factors related to high antibiotic prescribing in primary health care among children aged 0–6 years in the Capital Region of Denmark. *Scand. J. Prim. Health Care*, 34, 274–281. doi: 10.1080/0 2813432.2016.1207145.
14. Verbakel, J.Y.J., De Burghgraeve, T., Van Den Bruel, A., Coenen, S., Anthierens, S., Joly, L., Laenen, A., Luyten, J. and De Sutter, A. 2022. Protocol: Antibiotic prescribing rate after optimal near-patient C-reactive protein testing in acutely ill children presenting to ambulatory care (ARON project): protocol for a cluster-randomized pragmatic trial. *BMJ Open*, 12, 58912. doi: 10.1136/ BMJOPEN-2021-058912.

15. van Houten, C.B., Cohen, A., Engelhard, D., Hays, J.P., Karlsson, R., Moore, E., Fernández, D., Kreisberg, R., Collins, L. V., de Waal, W., *et al.* 2019. Antibiotic misuse in respiratory tract infections in children and adults – a prospective, multicentre study (TAILORED Treatment). *Eur. J. Clin. Microbiol. Infect. Dis.*, 38, 505–514. doi: 10.1007/s10096-018-03454-2.

16. van der Velden, A.W., van de Pol, A.C., Bongard, E., Cianci, D., Aabenhus, R., Balan, A., Böhmer, F., Lang, V.B., Bruno, P., Chlabicz, S., *et al.* 2022. Point-of care testing, antibiotic prescribing, and prescribing confidence for respiratory tract infections in primary care: a prospective audit in 18 European countries. *BJGP Open*, 6. doi: 10.3399/BJGPO.2021.0212.

17. Saust, L.T., Bjerrum, L., Arpi, M. and Hansen, M.P. Quality indicators for the diagnosis and antibiotic treatment of acute respiratory tract infections in general practice: a RAND Appropriateness Method. doi: 10.1080/02813432.2017.1333305.

18. Kip, M.M.A., Hummel, J.M., Eppink, E.B., Koffijberg, H., Hopstaken, R.M., IJzerman, M.J. and Kusters, R. 2019. Understanding the adoption and use of point-of-care tests in Dutch general practices using multi-criteria decision analysis. *BMC Fam. Pract.*, 20, 8. doi: 10.1186/s12875-018-0893-4.

19. Li, E., Dewez, J.E., Luu, Q., Emonts, M., Maconochie, I., Nijman, R. and Yeung, S. 2021. Role of point-of-care tests in the management of febrile children: a qualitative study of hospital-based doctors and nurses in England. *BMJ Open*, 11, 44510. doi: 10.1136/bmjopen-2020-044510.

20. 20. Donà, D., Barbieri, E., Brigadoi, G., Liberati, C., Bosis, S., Castagnola, E., Colomba, C., Galli, L., Lancella, L., Lo Vecchio, A., *et al.* 2025. State of the Art of Antimicrobial and Diagnostic Stewardship in Pediatric Setting. *Antibiotics*, 14, 1–31. doi: 10.3390/antibiotics14020132.

21. Dewez, J.E., Pembrey, L., Nijman, R.G., del Torso, S., Grossman, Z., Hadjipanayis, A., Van Esso, D., Lim, E., Emonts, M., Burns, J., *et al.* 2022. Availability and use of rapid diagnostic tests for the management of acute childhood infections in Europe: A cross-sectional survey of paediatricians. *PLoS One*, 17, 1–22. doi: 10.1371/journal.pone.0275336.

22. Dumpis, U., Hahlin, A., Varvuolyte, S., Stenmark, S., Veide, S., Valinteliene, R., Jurkeviciene, A. and Struwe, J. 2018. Antibiotic prescription and clinical management of common infections among general practitioners in Latvia, Lithuania, and Sweden: a pilot survey with a simple protocol. *Eur. J. Clin. Microbiol. Infect. Dis.*, 37, 355–361. doi: 10.1007/s10096-017-3141-2.

23. Dewez, J.E., Nijman, R.G., Fitchett, E.J.A., Lynch, R., de Groot, R., van der Flier, M., Philipsen, R., Vreugdenhil, H., Ettelt, S. and Yeung, S. 2023. Adoption of C-reactive protein point-of-care tests for the management of acute childhood infections in primary care in the Netherlands and England: a comparative health systems analysis. *BMC Health Serv. Res.*, 23. doi: 10.1186/S12913-023-09065-8.

24. Llor, C., Plate, A., Bjerrum, L., Gentile, I., Melbye, H., Staiano, A., van Hecke, O., Verbakel, J.Y. and Hopstaken, R. 2024. C-reactive protein point-of-care testing in primary care–broader implementation needed to combat antimicrobial resistance. *Front. Public Heal.*, 12, 1–11. doi: 10.3389/fpubh.2024.1397096.

25. Rebnord, I.K., Sandvik, H., Mjelle, A.B. and Hunskaar, S. 2017. Factors predicting antibiotic prescription and referral to hospital for children with respiratory symptoms: Secondary analysis of a randomised controlled study at out-of-hours services in primary care. *BMJ Open*, 7, 1–8. doi: 10.1136/bmjopen-2016-012992.

26. Sa, S., Aabenhus, R., Llor, C., Fournaise, A., Olsen, O. and Kj, J. 2022. in people with acute respiratory infections in primary care (Review). doi: 10.1002/14651858.CD010130.pub3. www.cochranelibrary.com.

27. Van Hecke, O., Bjerrum, L., Gentile, I., Hopstaken, R., Melbye, H., Plate, A., Verbakel, J.Y., Llor, C. and Staiano, A. 2023. Guidance on C-reactive protein point-of-care testing and complementary strategies to improve antibiotic prescribing for adults with lower respiratory tract infections in primary care. *Front. Med.*, 10. doi: 10.3389/fmed.2023.1166742.

28. Cooke, J., Llor, C., Hopstaken, R., Dryden, M. and Butler, C. 2020. Respiratory tract infections (RTIs) in primary care: narrative review of C reactive protein (CRP) point-of-care testing (POCT) and antibacterial use in patients who present with symptoms of RTI Respiratory infection. *BMJ Open Resp Res*, 7, 624. doi: 10.1136/bmjresp-2020-000624.

29. van Hecke, O., Raymond, M., Lee, J.J., Turner, P., Goyder, C.R., Verbakel, J.Y., van den Bruel, A. and Hayward, G. 2020. In-vitro diagnostic point-of-care tests in paediatric ambulatory care: A systematic review and meta-analysis. *PLoS One*, 15. doi: 10.1371/journal.pone.0235605.

30. Dumpis, U., Dimina, E., Akermanis, M., Tirans, E. and Veide, S. 2013. Assessment of antibiotic prescribing in Latvian general practitioners. *BMC Fam. Pract.*, 14, 9. doi: 10.1186/1471-2296-14-9.

31. Lemiengre, M.B., Verbakel, J.Y., Colman, R., Van Roy, K., De Burghgraeve, T., Buntinx, F., Aertgeerts, B., De Baets, F. and De Sutter, A. 2018. Point-of-care CRP matters: normal CRP levels reduce immediate antibiotic prescribing for acutely ill children in primary care: a cluster randomized controlled trial. *Scand. J. Prim. Health Care*, 36, 423–436. doi: 10.1080/02813432.2018.1529900.

32. Kirkwood, B.R. and Sterne, J.A.C. 2010. Essential Medical Statistics 2nd ed. Wiley-Blackwell.

33. Annette J. Dobson, A.G.B. 2018. An Introduction to Generalized Linear Models. *An Introd. to Gen. Linear Model. Fourth Ed.*, 10.1201/9781315182780. doi: 10.1201/9781315182780.

34. Leyland, A.H. and Groenewegen, P.P. 2020. Multilevel Modelling for Public Health and Health Services Research. *Multilevel Model. Public Heal. Heal. Serv. Res. Heal. Context*, 10.1007/978-3-030-34801-4. doi: 10.1007/978-3-030-34801-4.

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