# Laboratory tests in out-of-hours services in Norway

Studies with special emphasis on use and consequences of C-reactive protein test in children

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The candidate has been enrolled in the doctoral education programme at the Faculty of Medicine and Dentistry at the University of Bergen, Norway. The scientific environment has been the Department of Global Public Health and Primary Care at the University of Bergen

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# 1. Acknowledgements

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The Norwegian Medical Association's Funds for Research in General Practice have financially supported my project. I am very grateful.

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# 2. Abbrevations

| | |
|---|---|
| ALAT: | Alanin aminotransferase |
| ATC: | Anatomical Therapeutic Chemical classification system |
| CK-MB: | Creatinine Kinase MB Isoenzym (Myocardium) |
| CRP: | C-reactive protein |
| DDD: | Defined daily dose |
| ECG: | Electrocardiogram |
| EMCC: | Emergency Medical Communication Centre |
| ESR: | Erythrocyte sedimentation rate |
| GGT: | Gamma-glutamyl transferase |
| GP: | General practitioner |
| HbA1c: | Glycated hemoglobin |
| HELFO: | Norwegian Health Economics Administration |
| Hib: | Haemophilus influenzae type B |
| HP test: | Helicobacter pylori test |
| ICPC: | International Classification for Primary Care |
| INR: | International normalized ratio |
| Monospot: | Rapid test for infectious mononucleosis due to Epstein–Barr virus |
| MSIS: | Norwegian Surveillance System for Communicable Diseases |
| NKLM: | National Centre for Emergency Primary Health Care |
| NOKLUS: | Norwegian Quality Improvement of Primary Health Care Laboratories |
| OD: | Doctors working in OOH-services, but not employed as regular general practitioner. |
| OOH: | Out-of-hours |
| PC: | Pneumococcal conjugate |
| PcV: | Phenoxymethylpenicillin |
| RGP: | Regular general practitioner |
| Strep A: | Rapid test for Streptococcus A antigen detection |
| u-HCG: | Urine test of Human Chorionic Gonadotropin (Rapid pregnancy test) |
| UK: | The United Kingdom |

| | |
|---|---|
| WHO: | World Health Organization |

# 3. Abstract

## 3.1 English summary


**Background**

Children with infections and respiratory symptoms have the highest contact rate with Norwegian out-of-hours (OOH) services, especially in the youngest age group, and during the winter season. Many contacts are non-urgent in a strict medical sense. On-site measurement of C-reactive protein (CRP) is the most frequent laboratory test in Norwegian OOH, used in 60% of all contacts with children with infections and respiratory diseases. The aim of CRP is to differentiate between bacterial infections, viral and/or non-serious infections and to keep the use of antibiotics as low as possible. Nevertheless, the use of antibiotics has increased since the test was introduced as a point of care test until 2013. Several studies have investigated the diagnostic value of laboratory tests for children with fever, but not in primary health care where the prevalence of serious bacterial infections is low.

**Objective**

1. Investigate the use of laboratory tests at Norwegian out-of-hours services and which characteristics of the doctor, patient, diagnoses and geography that affects it.
2. Compare the RGPs' rate of CRP use at daytime and at OOH in consultations with children.
3. Evaluate if pre-consultation CRP screening affects the choice of treatment
4. Identify predictors for prescription of antibiotics and referral to hospital for children at OOH services.

**Design/method**

The first and second papers are from two cross-sectional registry based studies, based on electronic compensation claims from consultations in primary care. The third

study (third paper) was a randomized controlled observational study at OOH-services in Norway, including children < 7 years, presenting fever and/or respiratory symptoms to an OOH-service or a paediatric emergency unit. Every third child was randomized to a CRP test before the consultation, for the rest CRP was taken at request. The data consists of clinical examination results and questionnaire to parents. The fourth paper is an observational study based on data from the same study.

**Results**

**Paper I:** A CRP test is administered in 31% of all consultations OOH, for children with respiratory infections in 55%. Young doctors and doctors at central OOH services use the test most often.

**Paper II:** All RGPs use the CRP test more frequently OOH than in daytime practice; moreover, a high use at daytime indicates a high use OOH.

**Paper III:** In the group pretested with CRP, the antibiotic prescription rate was 26%, compared with 22% in the control group, there was no significant difference. Predictors for ordering a CRP test were a high fever at the consultation and the parents' opinion that their child needed antibiotics.

**Paper IV:** Main predictors for prescription of antibiotics were CRP values > 20 mg/L, signs on ear examination and use of paracetamol during the previous 24 hours. A high respiratory rate, low oxygen saturation and signs of auscultation were predictors for referral to hospital. In addition, parents' assessment of the seriousness was significantly associated with prescription of antibiotics and referral to hospital.

**Conclusion**

**Paper I and II:** CRP is extensively used at Norwegian OOH services and the differences in use cannot be explained by different diagnoses.

**Paper III:** CRP screening of children with fever or respiratory symptoms will not reduce the prescription of antibiotics.

**Paper IV:** Predictors for prescription are signs on ear examination, slightly elevated CRP values and the parents' assessment. Disturbed respiration is the most important sign predicting hospital admission.

## 3.2 Norwegian summary – norsk sammendrag

**Bakgrunn**

Små barn med infeksjoner har høyest kontaktrate på legevakt og CRP er den hyppigst brukte hurtigtesten. Testen brukes for å differensiere mellom bakterielle/alvorlige infeksjoner og virale/selvbegrensende infeksjoner, men den diagnostiske verdien er uklar. Ulike studier har forsøkt å belyse den diagnostiske verdien av laboratorieprøver for barn med feber, men få er utført i primærhelsetjenesten hvor det er lav prevalens av alvorlige bakterielle infeksjoner. Antibiotikabruken var likevel stigende frem til 2013.

**Hovedmål ved avhandlingen**

1. Kartlegge diagnostisk laboratorieutstyr på legevaktene, omfang av bruken og hvilke karakteristika ved lege, pasient, diagnose og geografi som påvirker bruken.
2. Sammenligne fastlegers bruk av CRP på barn i egen praksis og på legevakt.
3. Evaluere om screening med CRP før konsultasjonen har betydning for valg av behandling.
4. Identifisere faktorer som predikerer forskrivning av antibiotika og innleggelse i sykehus hos barn på legevakt.

**Design/metode**

Avhandlingens to første artikler er registerbaserte tverrsnittsstudier.

Tredje artikkel er en randomisert kontrollert observasjonsstudie på legevakt/akuttpoliklinikk. Hvert tredje barn med feber og/eller respiratoriske symptom fikk tatt CRP i forkant av legekonsultasjonen (intervensjonsgruppen). Øvrige barn (kontrollgruppen) fikk tatt CRP på indikasjon. Kliniske data ble hentet fra spørreskjema til foreldre, målinger utført av sykepleier og fra journalnotatet. Fjerde artikkel er en observasjonsstudie basert på data fra samme studie.

**Resultat**

**Artikkel:** CRP brukes ved 31% av alle legevaktkonsultasjoner, 55% hos barn med luftveissykdom. Yngre leger på sentrale legevakter og med høy vakthyppighet har høyere bruk.

**Artikkel II:** Alle fastleger bruker CRP oftere på legevakt enn på dagtid men høyt forbruk på dagtid indikerer også høyt forbruk på legevakt.

**Artikkel III:** 401 barn inkludert. Høy feber på konsultasjonstidspunktet og foreldre som tror barnet trenger antibiotika predikerer bruk av CRP. 26% av barna som fikk tatt CRP på forhånd fikk antibiotika mot 22% i kontrollgruppen. Forskjellen er ikke signifikant.

**Artikkel IV:** CRP > 20 mg/L, funn ved otoskopi og bruk av paracetamol siste døgn predikerer forskrivning av antibiotika. Forhøyet respirasjonsrate, redusert oksygenmetning og funn ved auskultasjon predikerer innleggelse i sykehus. Foreldrenes formening om barnets tilstand var signifikant assosiert med forskrivning av antibiotika og innleggelse.

**Konklusjon**

**Artikkel I og Artikkel II***:*

CRP er den dominerende hurtigtesten på legevakt. Store forskjeller i bruken av CRP mellom leger på legevakt kan ikke forklares ut fra ulike diagnoser.

**Artikkel III:** CRP screening av alle barn med feber og/eller symptomer fra respirasjonssystemet vil ikke redusere forskrivningen av antibiotika.

**Artikkel IV:** Funn ved otoskopi, lett forhøyet CRP og foreldrenes formening om tilstanden predikerer økt bruk av antibiotika. Respirasjonsbesvær predikerer innleggelse i sykehus.

# 4. List of publications

**Paper I**

Rebnord I, Sandvik H, Hunskaar S. Use of laboratory tests in out-of-hours services in Norway. Scand J Prim Health Care 2012; 30: 76-80.

**Paper II**

Rebnord I, Hunskaar S, Gjesdal S, Hetlevik O. Point-of-care testing with CRP in primary care: a registry-based observational study from Norway. BMC Fam Pract 2015; 16: 170.

**Paper III**

Rebnord IK, Sandvik H, Mjelle AB, Hunskaar S. Out-of-hours antibiotic prescription after screening with C reactive protein: a randomized controlled study. BMJ Open 2016; 6: e011231.

**Paper IV**

Rebnord IK, Sandvik H, Mjelle AB, Hunskaar S. Factors predicting antibiotic prescription and referral to hospital for children with respiratory symptoms: secondary analysis of a randomized controlled study at out-of-hours services in primary care. BMJ Open 2017; 6: e012992.

# 5. Introduction

## 5.1 Organization of Norwegian emergency primary care services

### 5.1.1 Out-of-hours services

The Norwegian primary care system is based on regular general practitioners (RGPs) contracted to the municipalities in a patient list system. RGPs work together in small or larger daytime practices, providing basic care and serving as a gatekeeper to secondary care. Mean list size is 1128 patients, mean age of the doctor is 48 years and 41% are female, totally there are 4600 RGPs per 2015 (1). The municipalities are also responsible for organizing an emergency primary care service, available for all inhabitants 24/7, called out-of-hours (OOH) services. The OOH organization varies from a single doctor on call in smaller municipalities to larger cooperatives serving two or more municipalities or larger cities (2). Normally an OOH cooperative is formed as a casualty clinic where also the community emergency medical communication centres are located, but the communication centres may also be located in a nursing home or in the Emergency Medical Communication Centre (EMCC) at the hospital (3). There have been trends towards larger inter-municipal OOH districts, an increase from 54% in 2009 to 58% in 2014 and a reduction in total number of OOH districts in the same period (3).

### 5.1.2 Staffing of the services

In small municipalities, only one doctor on call serves the population's acute emergency services. About 40% of all OOH services are organized in this way. For the remaining clinics 30-33% have one nurse on duty and 23-25% have more than one nurse. Only 5% have other personnel such as health secretaries working alone. Combinations of different organization and staffing are common at different times of day, since the clinic is often located in the RGPs office (3).

The RGPs are obliged to take part in the OOH service in the municipality with which they have a contract. However many RPGs do not participate at all and the participation varies a lot between OOH districts. RGPs in central and large municipalities participate less, including female and elderly RGPs. From a survey in 2007 in which 78% of all RGPs responded, 50% participated fully, 15% partly and 35% did not participate (4). From the reports based on the claims from doctors to the Norwegian Health Economics Administration (HELFO) the RGPs sent 55% of all claims in 2015 and only 20% of contacts were with doctors who were approved GP specialists (5). Other doctors (OD) are permanently staffed doctors with the OOH-service as their primary employer, temporarily employed doctors in training, hospital doctors taking extra jobs and other employment.

### 5.1.3 Funding of the services

The municipality is responsible for the basic remuneration of the staff and for providing them appropriate office facilities and equipment. The nurses at the clinics are employed and paid by the municipality. For the RGPs, the situation is different; the daytime practices and OOH services are mainly financed by a fee-for-service system. They send a claim to HELFO for each patient contact with information about the contact type, daytime or OOH and a fee for laboratory tests or procedures if it has taken place. There is one basic fee for all laboratory tests, in addition specific fees for specific tests analysed at the clinic as near patient tests. The available tests that have their own fee are: ECG, INR, HbA1c, Glucose, CRP, Strep A, u-HCG, Monospot, Hematological analysis with blood counter, Urine Culture, Fecal blood test, Microalbuminuria, Chlamydia test, Cholesterol, Potassium, Creatinine, GGT, ALAT, Glucose tolerance test, HP test, Microscopic examination. The RGPs are mainly responsible for their own costs at daytime practices, but for OOH services, the municipality is more frequently responsible for the costs. This activity-based remuneration system may affect both the RGPs and the use of the tests and procedures. A study from 2012 found this system to have a selection effect on potential GP recruits, attracting income-motivated men (6). It likely also affects the use of tests. One Norwegian study from 1992 from general practice found that the use of laboratory tests varied a lot and the activity-based remuneration system was one factor affecting it (7).

## 5.2 Diagnostic equipment in primary health care

### 5.2.1 Near-patient testing

Near-patient testing (also known as point-of-care testing) is defined as an investigation conducted at the time of the consultation with instant availability of results to make immediate and informed decisions about patient care (8). During the 1980s, more analytical tests became available for near-patient-testing in primary care. The benefits seemed obvious, earlier it could take from days to a week to get the same results when the blood sample had to be sent and analysed in an external laboratory/hospital. A survey study from Norwegian general practice in 1994 found that a diversity of instruments and test methods were in use and made quality assurance difficult. Group practices had a larger repertoire than solo practices and the GP's payment form did not influence the repertoire (9). A systematic review from 1999 concluded that available research provided little evidence on the effect of near patient testing on patient outcomes and the cost-effectiveness (8). Ten years later it was still claimed that near patient testing needed rigorous evaluations (10) while others argue that there has been some progress in this evaluation, especially for acute conditions (11).

Patient satisfaction was studied in a randomized controlled study from Australia in 2010. The results from this trial found a high degree of patient satisfaction and acceptability of near-patient testing in a general practice setting (12).

The clinicians' attitude towards near patient testing is described in a systematic review from 2011 (13). Clinicians found benefits of introducing such testing; increased diagnostic certainty, more efficient care and fewer re-consultations. But they also had some concerns about the accuracy of the tests in a primary care population, the impact of the GPs' role and costs and funding. Definitions of what situations and patients the tests were useful for was also called for.

Near patient testing has some clear benefits. The results are immediately available for the GP and the patient, and they may help the GP in deciding the treatment to be given. In acute situations such as at OOH services, this is clearly a great benefit where there is no follow-up or controls of patients. The GP must take an immediate decision during the consultation: medications or no medications, referral to hospital or wait-and-see. When the results are ready in minutes, it is very effective, has little delay and no need to follow up. However the utility of the tests depends on their ability to improve patient care (14). First, the quality of tests performed at the OOH services should be on a par with those conducted at other laboratories. In Norway, the organization Norwegian Quality Improvement of Primary Health Care Laboratories (Noklus) ensures that all laboratory analyses ordered, performed and interpreted outside hospitals will safeguard the patients' need for investigation, treatment and follow-up (15). Through membership, Noklus offers access to internal quality control procedures and an external quality control assessment programme, as well as advice on selecting methods and apparatus. Second, tests for a specific situation or condition should also include a threshold that results in a treatment or decision that will result in some difference for the patient. Examples: treatment with antibiotics is important for this type of infection, or referral to hospital for treatment of lung embolism is very important. Finally, many factors will influence the decision threshold. The pre-test probability of diseases should be estimated before taking the test and an evaluation of what is most important: to treat patients with the disease or not to treat those with no disease. If the first situation is important, to not overlook diseases, a test with high sensitivity is needed. In the other situation when it is important to not treat patients with no disease, high test specificity is needed (14).

Moreover, prevalence of the disease will affect the predictive value of the test. The same test with same sensitivity and specificity used in populations with different prevalence of the disease will give different predictive values. If the prevalence is low for a disease the positive predictive value will also be lower in this population (16-18).

### 5.2.2 Available equipment at the out-of-hours services

Near-patient testing at office laboratories has expanded in Scandinavian countries and the USA since the 1980s (8, 19-21). Urine analysis, blood sugar, haemoglobin, CRP, strep A test, INR and HbA1c are daily in use. Earlier most OOH-services shared facilities with daytime practices. This organization is now declining (3) but it is still the most usual organization model. The National Centre for Emergency Primary Health Care (NKLM) conducted a survey in 2009 to investigate the availability of diagnostic equipment, laboratory tests, medication and quality assurance system at all Norwegian OOH-services (22). We got an answer from 231 services (86%). Services located in GP surgeries with a daytime-practice had a wider range of equipment, laboratory tests and medicines. Physicians on duty in the OOH services with shared facilities did much of the laboratory work, but the personnel did the quality control during daytime. Some 27% of the independent services did not have external control of their laboratory work (not members of Noklus). X-ray, ultrasound apparatus and alcometer were rarely available, while more than 90% of OOH services had access to ECG, urine catheter, oto- and ophthalmoscope, as well as equipment for suture, gynecologic examinations and intravenous access. Six laboratory tests were available at almost all OOH services: CRP, blood sugar, urine dip stick, pregnancy test, streptococcus antigen test and haemoglobin. Only a few OOH services had the possibility to do clinical chemical analyses such as potassium, ALAT or creatinine. Quick tests for CK-MB, D-dimer and troponin were also rare.

### 5.2.3 C-reactive protein test; characteristics and challenges

C-reactive protein was discovered in 1930 and found to be an acute phase protein; an early indicator of infectious or inflammatory conditions (23). It has been widely used in hospitals to diagnose serious infections, monitor the effect of antibacterial treatment and differentiate between upper and lower respiratory or urinary tract infections. It has largely replaced the use of ESR (24) but it is also considered that its role in the decision making process is unclear (25). In the 1980s the test also became more important for primary care, especially after introduction of immunometric semi-quantitative methods for rapid test of CRP concentration (26). Since then, the test methods have been improved and now give exact values of the concentration in a few minutes, and use of the test has increased. Statistics are available from 2006: in 2006 it was used for 28% of all consultations at the OOH, in 2015 for 37% of all consultations (5).

Many studies have been published during the past fifteen years about CRP, its characteristics, benefits and limitations (13, 25, 27-35). A systematic review from 2005 evaluated the diagnostic accuracy of CRP in detecting radiologically proved pneumonia and evaluated how well it could discriminate between bacterial and viral infections in lower respiratory tract. Sensitivities varied from 8% to 99% and specificities from 27% to 95%. The conclusion was that CRP was neither sensitive nor specific enough to rule out or confirm bacterial aetiology of lower respiratory infections (36).

A review from 2011 concluded that combining CRP, procalcitonin and urine analysis were most valuable in identifying serious infections in febrile children (37). Different cut-off values should be used depending on whether one wanted to confirm or rule out serious infections. In this review from emergency departments with a prevalence of 20% of serious infections, the sensitivity was estimated at 40–50% with a CRP cut-off value of 80 mg/dl to confirm serious infections. To rule out serious infections, the cut-off value was set to 20 mg/dl. The sensitivity was then 80% but the specificity was only 70%. A prospective study from OOH services in the Netherlands published in 2016 evaluated whether these cut-off values could be used in a primary care setting to diagnose children at risk for a serious infection (38). They found that CRP had little clinically relevant value in discriminating febrile children in need of medical care from those with no need.

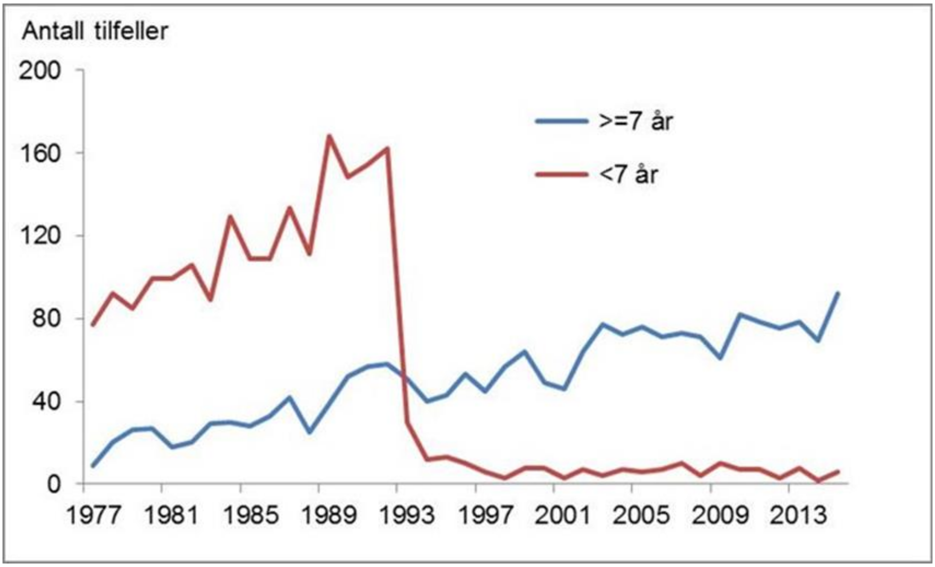
The major problem with CRP in these studies is the low sensitivity and specificity. They depend on the prevalence of the disease and the cut-off value that is used. No exact cut-off values are validated for use in primary care where the prevalence of serious infections is low.

## 5.3 Child health in Norway

### 5.3.1 Prevalence of serious infections and vaccination status

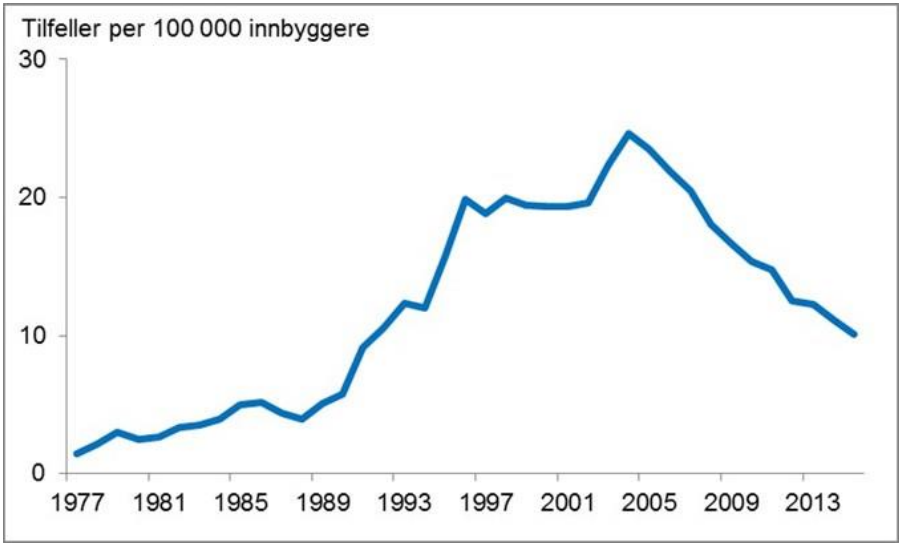
Infections were previously one of the main causes of infant mortality in Norway as in the world at large. More than 90 percent of children who die before the age of 18 die before the age of five (39). Children aged 0-5 years are most vulnerable. In the period 2000–2012, the mortality rate for boys was from 2.6 to 4.6 per 1,000 live births and for girls from 1.7 to 3.3. The most frequent cause of death in the first year of life is congenital diseases and malformations; infections are rare, totally 0–4 per year during the past 5 years in Norway (40). Yet infections are the most common reasons why parents contact primary care (5, 41). Viral self-limiting respiratory tract infections are very common, while bacterial infections such as pneumonia, meningitis and urinary tract infections are rare. Nevertheless, they are feared because of the necessity for rapid diagnosis and treatment to avoid complications or deaths. Between these extremes are infections such as otitis and throat inflammation. Traditionally they are perceived as bacterial, but recent research has found that they are largely self-limiting and antibiotic therapy provides few benefits (42-47). One important reason for the decline in serious infections is the introduction of two vaccines. Haemophilus influenzae type B (Hib) infections was the most frequent cause of meningitis, epiglottitis and other invasive infections in young children in Norway before the vaccine was introduced in the childhood immunization in 1992. Hib especially infected children under five years old; 3–8% of the patients died, and a significant proportion got permanent handicaps such as hearing loss or mental retardation. In the period from 1989 to 1992, there were more than 200 cases of invasive Hib infection. After the vaccine was introduced, these infections practically disappeared (48).

**Figure 1. Number of invasive Hib infections in Norway notified to MSIS in 1977-2012 per year for different age groups. Source: Norwegian Institute of Public Health. http://www.fhi.no**




The incidence of invasive pneumococcal infection fell from 75 to around 10 cases per 100 000 inhabitants after the introduction of pneumococcal conjugate vaccines (PC) in 2006 (48).

**Figure 2. Number of invasive pneumococcal infections in Norway notified to MSIS from 1977-2015 per year. Source: Norwegian Institute of Public Health. http://www.fhi.no**




We define severe infections as; sepsis, meningitis, pneumonia, osteomyelitis, cellulitis, gastrointestinal infections with dehydration, pyelonephritis and bronchiolitis with severe obstruction (hypoxia). How frequently these occur outside hospital is not well studied in Norway. A Belgian study from general practice found the incidence of all infections in the age group 0-4 years to be 1.73 episodes per year. For serious infections the incidence was 0.02 per year in the period 1998-2002 (49). The incidence was highest among the youngest children and pneumonia was by far the largest diagnostic group. The World Health Organization (WHO) has estimated the incidence of pneumonia in developed countries to 0.05 episodes per child-year (50). A systematic review from 2010 has estimated the effectiveness of Hib and PC vaccines against pneumonia mortality. For radiologically confirmed pneumonia, the reductions were estimated to be 18 and 26%, respectively (51). Varying populations and interventions in different studies make such estimates difficult to measure.

Since pneumonia is the most frequent serious infections it is also important to know the aetiology of this disease. A recent study from Norway found that in radiologically proven pneumonias, the majority were viral infections; respiratory syncytial virus was predominant among the youngest, mycoplasma most common among older children and bacterial causes were rare (11%) (52). Other European countries have the same pattern in terms of aetiology (53, 54).

### 5.3.2 Prescription of antibiotics

Despite lower prevalence of severe infections, the total consumption of antibiotics has remained relatively stable over many years, but a gradual increase in consumption and a shift among the various subgroups is seen. In 2014, the overall sales of antibiotics for systemic use in humans amounted to 19.3 defined daily doses (DDD)/1 000 inhabitants/day. The use of macrolides has decreased since 2011, probably because of a Mycoplasma pneumonia epidemic during that year. The use of penicillins with extended spectrum has been stable while the use of betalactamase sensitive penicillins has decreased since 2011 (Figure 3). Approximately 85% of all DDDs are sold by prescriptions in primary care. Females use more antibiotics than males; 27% of the females purchased at least one antibiotic course in 2014 compared to 19% of the males. The highest use is found among young children, young women and the elderly (55).

In primary care, the elixirs with phenoxymethylpenicillin, amoxicillin, macrolides and clindamycin are the most commonly used antibiotics for children with fever / respiratory infections. The Norwegian Prescription Database shows the consumption in DDDs during the past 10 years for the age group 0-4 years alone (Figure 4). There has been a steady increase in consumption up to 2012, for the last 3 years a small decrease, the largest reduction for macrolides (48).

**Figure 3. Turnover by dosage (DDD) of different antibiotics per year for all ages. Source: Norwegian Prescription Database, Norwegian Institute of Public Health. http://www.reseptregisteret.no**

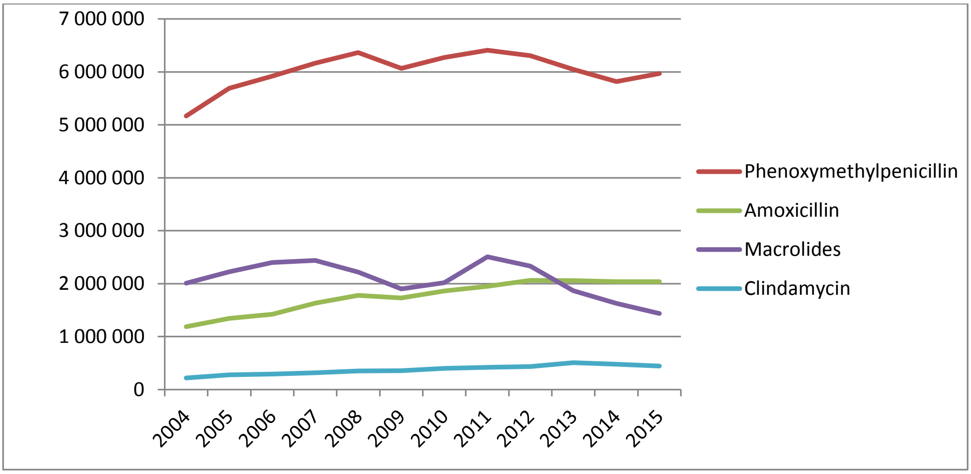
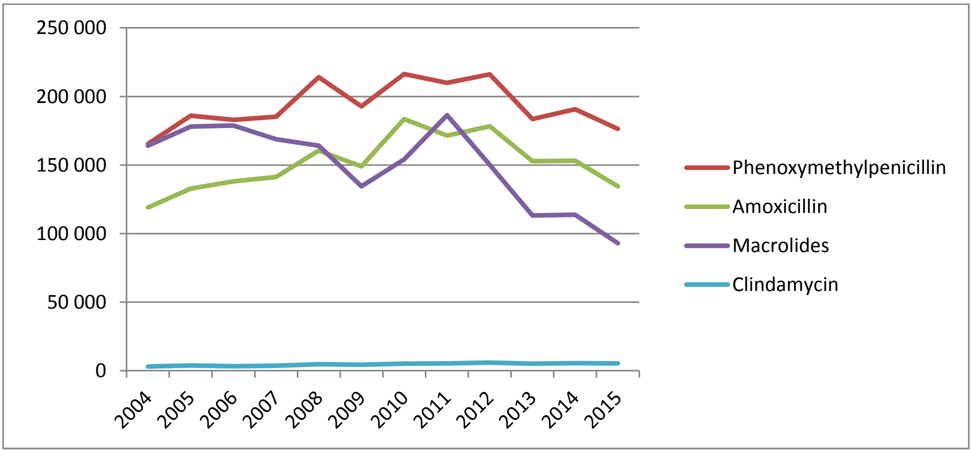



**Figure 4. Turnover by dosage (DDD) of different antibiotics per year for the age group 0-4 years. Source: Norwegian Prescription Database, Norwegian Institute of Public Health. http://www.reseptregisteret.no**



## 5.4 Comparisons with other countries

### 5.4.1 Organization of out-of-hours services and use of CRP in other European countries

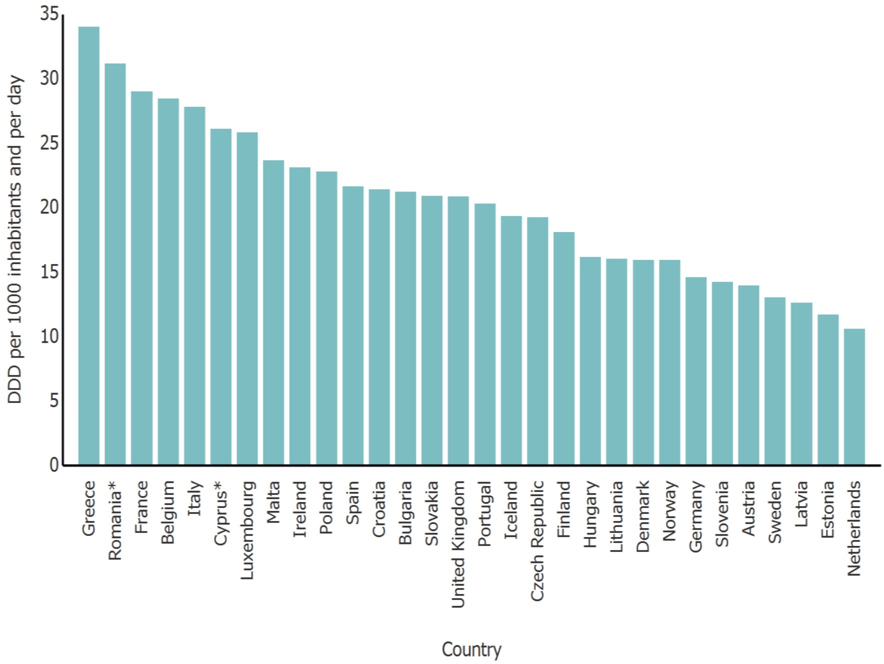
OOH services and primary care have different organizations in other European countries and comparisons may be difficult between countries. Some main differences:

- The organization and gatekeeper function: In Norway all patients are seen in primary care before referral, in most other countries patients can meet at the hospital directly even if it's not preferred. Most countries have special emergency departments for children at hospitals in cities, staffed by paediatricians.
- Different telephone triage system before consultations. Some countries use telephone-triage extensively, others just as a supplement and varying from place to place. In Norway telephone-triage by nurse is considered safe, 4 of 5 enquiries are correctly classified as acute, urgent or non-urgent (56).
- CRP as a near-patient-test is extensively used in Scandinavian countries, Switzerland and the USA, but to a limited extent in other European countries (8, 35, 57).

### 5.4.2 Comparison of prescription rate of antibiotics to children

The prescription rate of antibiotics varies a lot between countries and the differences cannot only be explained by different prevalence of sickness or mortality. Nordic countries have the lowest portion of broad-spectrum antibiotics compared to the rest of the European countries (58), an important strategy to prevent the development and increase in resistant microbes (59).

**Figure 5. Consumption of antibacterials for systemic use (ATC J01) in the community care sector in Europe in 2014. Source: European Centre for Disease Prevention and Control (accessed 14 november 2016) http://ecdc.europa.eu**




Children are a vulnerable group in relation to infections with multi-resistant microbes. Some European countries have focused on reducing prescription of antibiotics and in studies looked at predictors of prescribing and what measures can help to reduce prescription of antibiotics to children. The Netherlands has the lowest total prescription in Europe, and a well-developed primary health care with GPs working at the OOH-services. A study from 2012 using data from 322 consultations with febrile children found the prescription rate to be 36%. Main predictors were concerned parents, ill appearance, earache, signs of throat infections and decreased urine production (60). Another Dutch study tested febrile children for respiratory viruses and found that more than 50% were infected with at least one virus. The prescription rate was 37% and not associated with the outcome of viral testing (61). An Italian study of 284 children found a prescription rate of 23%. Determinants of prescription were young age and duration of illness (more than 5 days) (62). A recent study from the United Kingdom of 999 children at age <5 years with acute illness found a prescription rate of 26%. The strongest predictors were a clinician diagnosis of tonsillitis, ear infection, lower or upper respiratory infection and abnormal findings on chest, ear or throat examination. The diagnosis was more important than abnormal findings on examination. Clinician impression scale, a high age and poor sleep were also associated, but not the parents' impression of illness severity (63). None of these studies used CRP as a variable. A randomized trial introducing CRP to an OOH service in the UK including 200 children found the testing feasible and acceptable, but the total prescription rate was 30% and the CRP testing did not reduce the prescription or referral rate (64).

Sweden has the lowest consumption of antibiotics in Scandinavia. One study from primary care collecting data from 1999 until 2005 found that antibiotic prescription decreased in this period, mainly because of a decrease in the consultation rates for children. Especially the consultation rates for otitis media and sore throat declined. Near patient testing were used extensively; CRP was taken in 36% of consultations with respiratory infections and a strep-A test in 23%, often not in accordance with guidelines. The prescription rate rose with rising CRP values for the diagnoses of common colds and bronchitis (65). Another Swedish study explored how CRP supports GPs in their decision concerning antibiotic prescription. They found a general low prescription rate and high use of CRP testing. CRP influenced the GPs to change their decision about antibiotic prescriptions in patients with acute cough but did not reduce overall antibiotic prescribing by GPs who already had a low antibiotic prescribing rate (66).

Few studies from Norwegian primary health care have investigated children. One study from 2013 has studied the prescription pattern for respiratory infections in preschool children (67). The total prescription rate was 26%. Phenoxymethylpenicillin accounted for 42% and macrolides for 30%. Predictors for

prescription were the diagnoses (tonsillitis and pneumonia), age >2 year, not GP specialist and busy GPs.
A common purpose of all these studies is to reduce unnecessary prescribing of antibiotics while not overlooking serious infections that require further treatment. Factors that predict prescription vary in the different studies depending on the study design. Finding predictors that could be affected is important for the purpose of reducing prescription. The above-mentioned research demonstrates that aspects of the child, the parents' opinions, findings during examination and doctor's assessment of these all appear to affect prescribing. CRP is one of many factors that seem to be emphasized by many physicians, but in children it is not yet well documented that the test reduces prescription.

Some qualitative studies have also investigated prescription patterns. One systematic review from 2015 found that a high degree of uncertainty existed among parents and clinicians. Clinicians often reported use of "just in case" prescription and felt pressure from parents. Parental concern may be misinterpreted as a desire or demand for a prescription. Parents in turn sought a thorough medical evaluation by a physician they could trust and were concerned about getting the right information and advice about treatment (68). A study from Sweden interviewed GPs that were not following current guidelines for sore throat in their decision-making. They found that inappropriate use of the near-patient tests could partly be understood as remnants of outdated knowledge. New guidelines and technologies should be introduced with better information. In addition, consequences of introducing new tests in the clinical everyday work should be better assessed (69).

Education of clinicians and patients/parents has been studied in different studies (70-72). One systematic review from 2016 found that educational interventions were effective in reducing antibiotic prescription for childhood upper respiratory infections, most effective when the intervention was addressed to both clinicians and parents (73). A study from Norwegian OOH services found that using trained GPs to give peer academic detailing to colleagues and an open discussion about prescription pattern showed significant changes in prescription of antibiotics towards the National Guidelines (74).

There are different prescribing patterns between countries and between clinicians (75). The complex picture of various factors affecting prescribing patterns of individual clinicians and the fact that prescription still should be reduced (76) imply that further research in this field is important.

### 5.4.3 Guidelines and clinical decision making systems for primary care

Guidelines are recommendations for clinical practice based on available evidence-based knowledge in specific fields (77, 78). A widely used definition is "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (79). A statement should be based on systematically collected and critically evaluated scientific evidence; they need to be updated regularly and easy available. The guidelines are recommendations. Clinicians also need to make use of their professional judgment: what is acceptable for patients and clinicians, available resources, economics and ethics. National health authorities have released countless different policies for different topics in both primary and secondary care. These are indicative and do not provide a basis for legal responses. The most used guideline for primary care and infections is “Antibiotic treatment in primary care” (80) which describes drug of choice for different infections.

The challenge doctors face in consultations with children who have infections is to distinguish between self-limiting infections and those requiring treatment. To treat bacterial infections that benefit from antibiotics and select those who need hospitalization is important. Clinicians always fear missing or ignoring a serious illness. Various decision support tools have been developed to avoid this. A severity-of-illness scoring system, often called clinical prediction rule or decision tree, where different clinical variables (symptoms and signs) and laboratory values give a score to guide for which measures one should take could be a useful tool in this context. A system has to be validated in the same way as laboratory tests and evaluated with respect to sensitivity and specificity. Also here, the prevalence of the disease becomes important; a prediction rule used in hospitals is not necessarily applicable to primary care with a lower prevalence of severe disease.

A systematic review from 2010 tried to identify clinical features that could be used in confirming or excluding the possibility of serious infection in children (81). The study highlights the difficulty of the diagnostic task facing clinicians responsible for identifying seriously ill children at initial presentation. Symptoms were categorized as red flags for serious infections; reduced consciousness, convulsions, cyanosis, rapid breathing, slow capillary refill, parental concern and clinician global impression, difficulty in feeding and temperature more than $40^{o}$ C. No single feature had a rule-out value but some combinations could be used for excluding the possibility. A Dutch observational study from general practice found that more than 50% of children had one or more alarming sign/symptoms and confirms the need of determining predictive values of alarming signs/symptoms (82). A more recent systematic review from 2012 found 35 studies, (83), only one from primary care (84). Several clinical features can increase or decrease the probability of serious infections but not sufficient on its own to raise or lower the risk. It illustrates the diagnostic gap between the predictive value from clinical features and the level of risk at which clinical action should be taken. This gap is often filled by using “gut-feeling” and diagnostic safety-netting, not well defined (85). The topic is summarized in an article from the same authors (Van den Bruel) in 2014: “Research into practice” (86). The focus should be at identifying children who can be safely managed in primary care.

Diagnostic tests assist either as a red flag marking serious infections as likely if positive or to rule out serious infections when negative. Currently, CRP lacks evidence of its being useful for children. The same symptom-based decision tree from Belgium primary care in 2007 (84) was validated in a new prospective study in

Belgium and published in 2015 (87). They found this clinical prediction rule to have a sensitivity of 100% but a specificity of 84% in a general practitioner setting, some lower sensitivity/specificity in emergency department/paediatric outpatient setting. An ongoing randomized trial from the same area now also have added the CRP-test and measurement of oxygen saturation to the same decision tree, results are not published yet (88).

# 6. Aims of the studies included in the thesis

The overall aim of this thesis was to investigate the use of diagnostic tests at OOH services in Norway and how it affects the decision-making and treatment of children with infections and respiratory symptoms. Three studies were carried out to achieve the aims and the results are published in four articles (**Paper I-IV**).

**Study I:**
To investigate to what extent laboratory tests are used at OOH and how it is affected by factors as diagnoses, geography and patients' or doctors' characteristics (**Paper I**).

**Study II:**
To investigate how the RGPs use CRP in daytime practice when the patient is a child and to compare it with the use at OOH-service. We also searched for associations between variations in the use and characteristics of the RGPs (**Paper II**).

**Study III:**
To evaluate the effect of pre-consultation screening with CRP on antibiotic prescription and referral to hospital for children 0-6 years in primary care with low prevalence of serious infections (**Paper III**).

To identify predictors for antibiotic prescription and referral to hospital in a primary care setting with children 0-6 years (**Paper IV**).

# 7. Study populations and methods

This section includes a brief description of the material and methods of the four articles presented. The first and second papers were registry-based observational studies. The third was a randomized controlled study and the fourth was an observational study based on the same material.

## 7.1 Study populations

- Study I: All electronic compensation claims from OOH in Norway in 2007 n=1 323 281.
- Study II: All electronic compensation claims from consultations with children 0-5 years during the period 2009–2011 in Norwegian primary care n=2 552 600.
- Study III: Children 0-6 years with fever and/or respiratory symptoms contacting OOH in 2013-2015 n=401.

## 7.2 Materials and methods of the individual studies

### 7.2.1 Study I (Paper I)

We collected all electronic compensation claims from doctors working in OOH services in Norway in 2007. The claims are sent electronically to the Norwegian Health Economics Administration (HELFO), which is responsible for remuneration. The file from HELFO was anonymized and contained the following variables: patient's age, gender, centrality of the municipality, diagnoses, doctor's age, sex, RGP or not, and the specific fees that indicate the type of contact (consultation or home visit) and procedures. All contacts have one or two diagnoses coded with the ICPC2 system (International Classification for Primary Care) and are used for both symptoms/complaints and diseases, infections and injuries. If a laboratory test is taken there is one basic fee used, in addition specific fees for some point-of-care tests, but not for e.g. haemoglobin, sedimentation rate and urine dip-stick tests. Centrality is defined as a municipality's geographical location in relation to central functions and is measured from 0-3, and 3 is most central. We had information about the doctor's age, sex and if he was working as a regular general practitioner (RGP). Doctors not working at daytime as RGPs are called 'other doctors' (OD). They may be locums, newly qualified doctors or temporary employed doctors who are working at daytime in hospitals or universities.

We have not included claims sent to HELFO on paper. In 2006 4,9% of the claims were sent on paper and in 2007 probably fewer. In addition some consultations at age group 12+ were paid solely by the patients and may not have been registered by HELFO if there was not used a laboratory fee or procedure fee. We have estimated this underreporting at 8% in this age group and almost nothing for younger children because of full reimbursement of all costs (89).

### 7.2.2 Study II (Paper II)

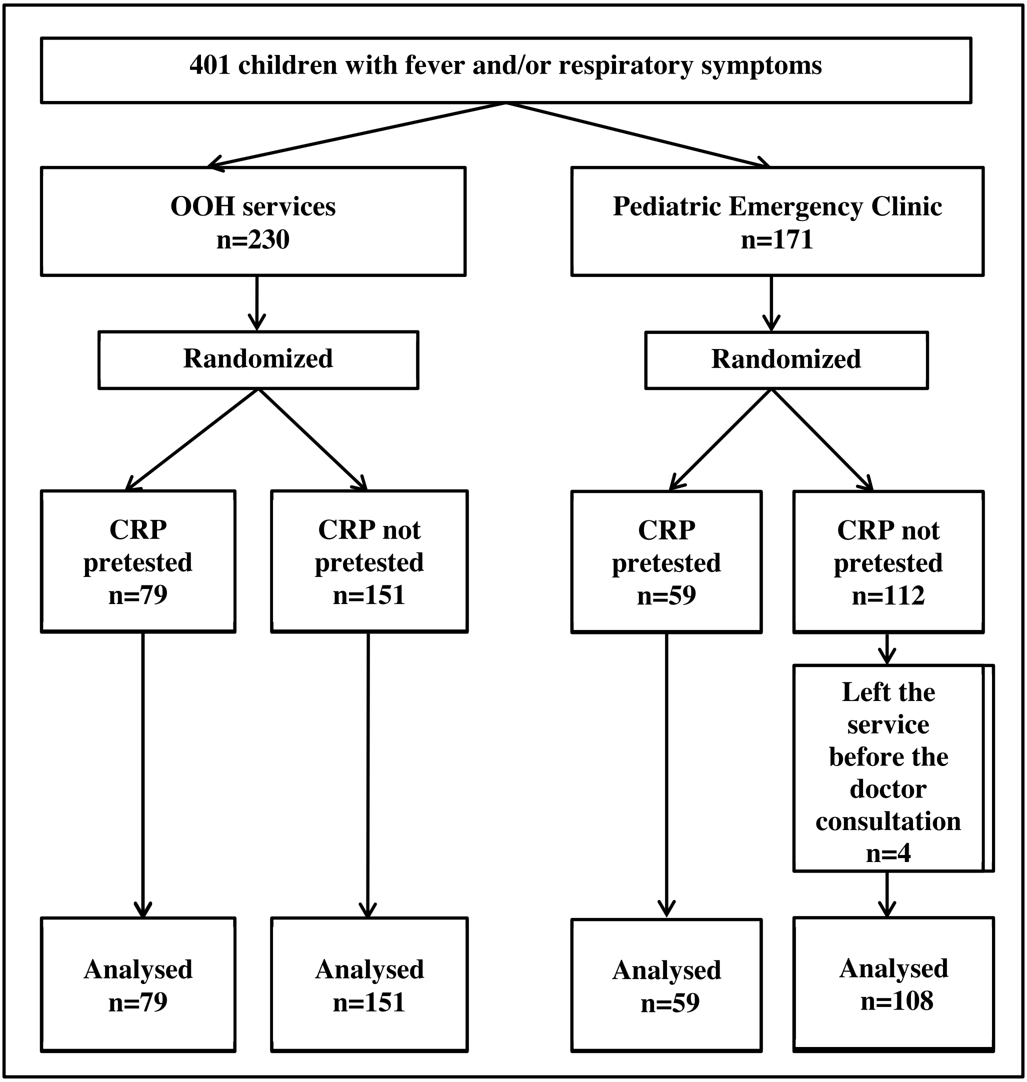
Electronic claims are also used in this study but from both OOH services and daytime practices in 2009, 2010 and 2011. We selected all consultations and accompanying laboratory tests for the age group 0-5 years. The claims included diagnoses coded by the ICPC-2 classification. This data file was linked with information from the national RGP database with information about the individual RGPs' age, gender, specialty, list size, whether the list was open for new patients and practice municipality. The selection of children was done to make a comparison of as similar patients as possible at daytime and OOH, to avoid older people with more chronic diseases. The RGP database had no information about doctors not working as a regular GP at daytime, so they are not included in all analyses. When comparing the RGP's practice in daytime and OOH, we included only RGPs with more than a total of 20 consultations with children during the study period both at daytime practice and at OOH service.

### 7.2.3 Study III (Paper III and Paper IV)

We included 401 children 0-6 years with fever and/or any respiratory symptoms during winter seasons 2013-2015 (Figure 6). All were recruited from four different OOH services outside Bergen: Askøy, Sotra, Samnanger/Os and Nordhordland. In addition, one paediatric emergency clinic at Haukeland University Hospital in Bergen participated. This clinic is a walk-in, open access facility, located at the hospital and staffed by paediatricians. Every third child was randomized to a CRP test before the consultation, the remaining 2/3 received usual care and the doctor could order a CRP test on individual indication. The data consist of clinical symptom and signs collected by a nurse at the clinic and a questionnaire filled in by the parents before the consultation. The nurses at all OOH services were informed about the study and about the form they had to fill out. At the emergency clinic, we had two trained nurses engaged especially for the project. The nurses collected the following variables from the medical history: age, gender, previous chronic disease, duration of present illness, fever during past 24 hours, variation in fever, vomiting, earache, coughing, dyspnoea, throat symptoms, diarrhoea, reduced diuresis, cervical rigidity, skin rash and use of paracetamol or ibuprofen during past 24 hours. An examination was also done by the nurse, measuring temperature, respiratory rate, oxygen saturation, degree of hydration, capillary refill time and general condition on a three-point scale (normal, ill and severely ill). On the questionnaire to the parents before the consultation, the nurse had to mark an assessment of the illness and its seriousness. Finally, we collected the medical record after the consultation with the two main outcome variables: antibiotic prescription and referral to hospital.

We used the same materials from the randomized study in the observational study and the same main outcome variables. All children were analysed as one group.

**Figure 6. Flowchart over included and investigated patients in the study.**



## 7.3 Statistical analyses

Statistical analyses were performed using IBM-SPSS Statistics version 18 (**Paper I**), 21 (**Paper II** and **Paper III**) and 23 (**Paper IV**). We used standard descriptive statistics to characterize the different background variables in all studies. Multiple logistic regression analyses were used in all papers to calculate odds ratio with 95% confidence intervals including explanatory variables significant in bivariate analyses. We compared proportions by Chi square tests, means by t-test. Significance level was set at 5% ($p<0.05$). Goodness-of-fit of the model was assessed by a Hosmer and Lemeshow test in **Papers II** and **IV**. Multiple imputations were done in paper IV to avoid missing cases in the multiple regression analyses.

## 7.4 Study sample calculation (Study III)

A study sample calculation was done before the randomized controlled trial (Study III). The power calculation was based on the following presumptions: we presumed that 35% of all children would receive antibiotic treatment based on data from earlier studies, and that CRP would be requested in every second consultation. Furthermore, we presumed that the doctor requested a CRP for the most seriously ill children and that 50% of these children would receive antibiotics, compared with 20% for the healthier non-tested group. The null hypothesis was that pretested CRP would not change the frequency of antibiotic treatment, that is, 35% of both groups would receive antibiotics. If a 40% change (effect size) in antibiotic treatment due to pretested CRP was defined as significant, using a two-sided test, power 80%, $\alpha$ level 5%, the sample sizes would have to be 130+259. If effect size were reduced from 40% to 20%, the sample sizes would have to be 525+1050. As it turned out, recruiting participants was challenging, and an interim analysis was performed when 400 children were included. The difference in antibiotic prescriptions was much smaller than what we considered clinically significant, and we therefore decided to stop further recruitment of participants.

## 7.5 Ethical assessments and approvals

### 7.5.1 Study I

HELFO and the Privacy Ombudsmann for Research (Norwegian Social Scientific Data Services) assessed the project.

### 7.5.2 Study II

HELFO and The Norwegian Data Protection Authority allowed the use and linkage of data. The Norwegian Directorate of Health, as register owner, also approved the linkage of registers.

As it is not possible to identify individuals in the material in Study I and Study II, directly or indirectly, the projects were not subject to obligatory notification.

### 7.5.3 Study III

This study was approved by the Regional Committee for Medical and Health Research Ethics (2012/1471/REK Vest). Informed written consent was obtained from all participants.

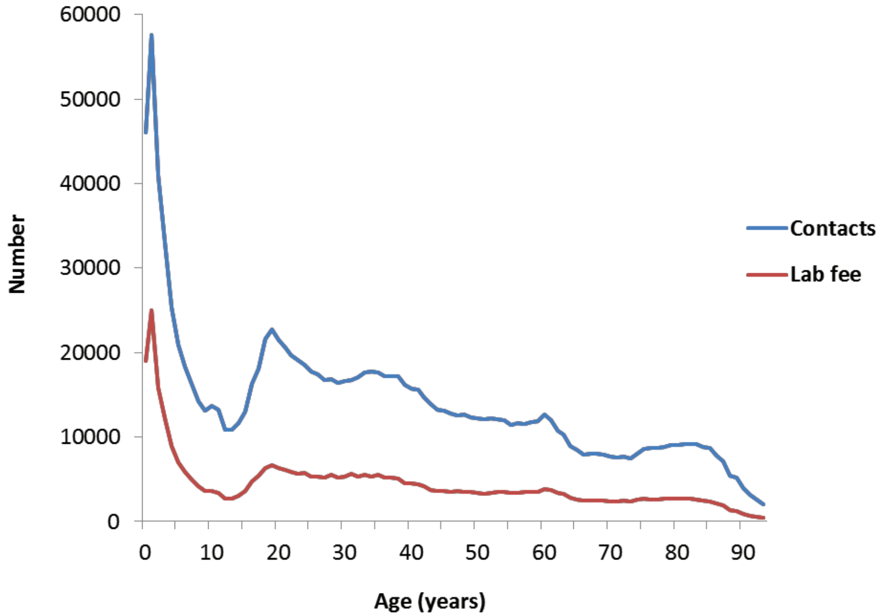
# 8. Summary of results

## 8.1 Paper I

**Use of laboratory tests in OOH services in Norway**

The material consisted of 1 240 235 claims from consultations and 83 046 from home visits. The number of contacts was highest for the age group 0-1 year and a smaller peak in the number of contacts around 20 years.

**Figure 7. Distribution of all contacts and laboratory fees per age group.**




A laboratory test was used in 31% of all contacts, and the distribution of laboratory claims by age was similar to the distribution of contacts. CRP test was predominant, used in 27% of all consultations, ECG was used in 4% and rapid Strep A test in 4%. Other tests were used in less than 2% of all consultations. In the age group 0-1 year, a CRP test was taken in 42% of all consultations and for respiratory disorders (24% of all contacts), CRP was used in 55%.

Mean age of RGPs was 44 years, for ODs 38 years. RGPs sent 47% of all claims, OD 53%. Female RGPs were younger (37 vs. 42 years) and sent 22% of all claims. We performed multiple regression analysis to find characteristics of the doctor using more laboratory tests. We found that younger doctors, female doctors and doctors working in central areas used laboratory tests significantly more often. Home visits were more frequent in rural areas than central areas (11% vs. 5%) but the use of CRP per home visit was less in more central areas.

## 8.2 Paper II

**Point-of-care testing with CRP in primary care: a registry-based observational study from Norway**

Results from **Paper I** indicated that CRP is the dominating laboratory test at OOH-services. This study compared the RGPs' rate of CRP use at daytime and OOH in consultations with children and how this rate was influenced by characteristics of the RGPs.

The materials consisted of 2 mill contacts at daytime and nearly ½ mill contacts at OOH with children 0-5 years during 2009 until 2011. CRP was used in 31% of all consultations and 44% of all OOH consultations. Respiratory diseases, infections and fever constituted 50% of all contacts at daytime and 59% of all contacts OOH. More than 80% of the total number of CRP tests were taken in these consultations and CRP was used in 44% and 58% of the daytime and OOH consultations respectively.

*RGPs use of CRP*

The mean rates of CRP use for the RGPs were significantly higher for all diagnoses OOH compared to daytime. Mean rate difference from daytime to OOH was 0.14 (CI 0.09-0.19, $p<0.001$). The RGPs' individual use of CRP from daytime to OOH was similar; high-users at daytime were high-users at OOH, and vice versa. Comparing the RGPs working both in daytime practice and OOH with RGPs working only at daytime, we found them to be younger, less often approved specialists in general practice, more often males and had fewer patients on their list. The rate of CRP use at daytime however was not significantly different. The distribution of diagnoses at ICPC chapter level was similar at daytime and OOH.

*Predictors for high usage of CRP tests*

To identify predictors for high usage of CRP we did a multiple regression analysis. The RGPs individual CRP rate (mean use of CRP per consultation) was distributed in quintiles and we used the fifth quintile as outcome variable representing high usage. At daytime a high rate of CRP was significantly associated with not approved RGPs, female RGPs, a larger list size and a larger number of consultations with children but fewer children on list. At OOH, the strongest predictor for high usage was a high use of CRP at daytime, OR 1.12 (CI 1.10-1.14) $p<0.001$. Also to being a young doctor and having a large number of consultations with children were factors significantly associated with high usage at OOH.

## 8.3 Paper III

**Out-of-hours antibiotic screening with C reactive protein: a randomized controlled study**

This study evaluated the effect of pre-consultation CRP screening on antibiotic prescribing and referral to hospital in a clinical setting in primary care.

We included 401 children but excluded 4 children because they left the clinic before the doctor consultation. The study analysed 171 subjects from the emergency clinic that were examined by a paediatrician and 230 from OOH services examined by an OOH doctor.

*Comparison of the randomized groups*

A total of 138 were randomized to a CRP test before the consultation; 263 were in the control group with usual care and the doctor could order a CRP test on medical indication as normal. No significant differences were found between the intervention and control group. We also made a comparison of the group at the emergency clinic and the OOH services. Children from the emergency clinic had significantly lower temperature and respiratory rate, less use of paracetamol, higher oxygen saturation and were assessed to be in better general condition than those at the OOH services. The total antibiotic prescription rate was 23% (93 children) and the referral rate was 8% (31 children). In the intervention group the prescription rate was 26% (CI 19-34) compared to 22% (CI 17-27) in the control group (p=0.361). The referral rate was 5% (CI 1-9) in the intervention group and 9% (CI 6-13) in the control group (p=0.138).

*Predictors for ordering a CRP test*

There were significant differences between OOH doctors and paediatricians in how often they ordered a CRP test if it was not pretested. Paediatricians ordered CRP in 9% of all cases, OOH doctors in 56% of all cases (p<0.001). In the logistic regression analyses, three variables were significantly associated with ordering a CRP: being an OOH doctor, a high measured temperature at the consultation and if parents thought their child had a serious infection.

*Distribution of diagnoses*

Upper respiratory infection was the most used diagnosis followed by otitis media and tonsillitis (table 1). The mean result of pretested CRP was significantly lower in the pretested group than in the control group where CRP was taken on request (21 vs 34 mg/L, p=0.006).

**Table1. Distribution of diagnoses, mean CRP values in pretested and taken on request group and how often CRP is taken on request.**

| Diagnoses | Distri-bution % n=397 | Mean CRP values (mg/L) Pretested group n=138 | Mean CRP values (mg/L) Taken on request group n=259 | CRP taken on request, % n=259 |
|---|---|---|---|---|
| Acute tonsillitis | 11.8 | 29 | 45 | 40.7 |
| Otitis media | 13.6 | 22 | 26 | 38.5 |
| Pneumonia | 3.8 | 49 | 86 | 80.0 |
| Upper respiratory infection | 48.9 | 17 | 29 | 32.3 |
| Fever/Cough | 8.0 | 9 | 38 | 50.0 |
| Bronchiolitis/Asthma | 7.8 | 13 | 14 | 22.7 |
| Pyelonephritis | 0.5 | - | 91 | 100.0 |
| Other | 5.5 | 14 | 11 | 43.8 |

## 8.4 Paper IV

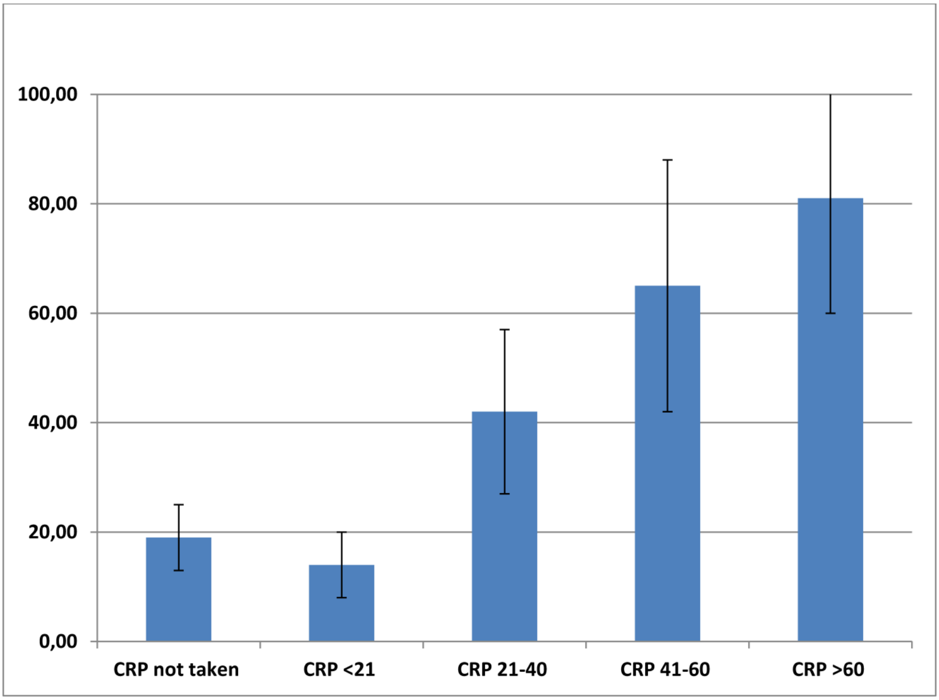
**Factors predicting antibiotic prescription and referral to hospital for children with respiratory symptoms: secondary analysis of a randomized controlled study at out-of-hours in primary care**

The first paper from this study (**Paper III**) found no significant effect of CRP screening on antibiotic prescription or referral to hospital. The aim in this paper was to identify predictors for prescribing and referral.

*Prescription of antibiotics*

In total 93 children (23%) got a prescription of antibiotics. Phenoxymethylpenicillin (PcV) was used in 67%, amoxicillin in 20% and macrolides in 9%. The distribution of diagnoses and prescription rates showed that for pneumonia all got antibiotics if not referred to hospital. For the other diagnoses, there was a clear tendency that a higher CRP value led to a higher prescription rate (Figure 8). If the parents thought it was a bacterial infection that needed treatment with antibiotics, 39% got a prescription. A Strep A test was used in seven children, all were negative. Three of them got a prescription of antibiotics, and they were diagnosed as tonsillitis, otitis media or URI.

**Figure 8. Antibiotic prescription rates (%) with 95% confidence interval at different CRP levels (n=366)**




Multiple regression analysis was used to find predictors. All explanatory variables significant in bivariate analyses were put into the analyses. For prescription of antibiotics we found that findings on ear examination (OR 4.62; 95% CI: 2.35, 9.10), use of paracetamol last 24 hours (OR 2.35, 95% CI 1.11, 4.96), CRP values > 20 mg/L (OR 3.57, 95% CI 1.43, 8.83) and parents' assessment that their child had a bacterial infection (OR 2.45, 95% CI 1.17, 5.13) were significantly associated. Vomiting last 24 hours was negatively associated (OR 0.25, 95% CI 0.13, 0.53).

*Referral to hospital*

In total 31 children (8%) were referred to hospital. When the parents assessed the child as needing hospitalization, 86% were referred to hospital. The strongest predictor for referral to hospital was affected respiration. A high respiratory rate (OR 1.07, 95% CI 1.03, 1.12), obstructive signs on auscultation (OR 5.57, 95% CI 1.11, 9.26) and reduced oxygen saturation (OR 3.39, 95% CI 1.02, 11.23) were all significantly associated. In addition, the parents' assessment of disease severity (OR 414, 95% CI 25, 6624) was significantly associated with referral. Findings on ear examination were negatively associated (OR 0.22, 95% CI 0.05, 0.87).

# 9. Discussion

## 9.1 Methodological considerations

This thesis is based on three separate studies presented in four papers. The two first studies are registry based observational studies and nearly the same databases are used, so I will discuss these studies together. The last study, a clinical, randomized trial, has other considerations and is therefore discussed separately.

### 9.1.1 Study I and II (Paper I and Paper II)

**Design**

In general, observational studies are used to look for the effect of exposure or risk factors on a disease or condition. There are limitations in interpreting associations as causal relationships in such studies because of confounding and what samples are used. We obtained data for our studies from HELFO. The strength is that we got nearly complete reports of activities from a whole year in **Paper I** and from three years in **Paper II** from the whole country. Because of the strong economic motivation for doctors to send the claims for remuneration, missing data is a minor problem. Also paper based claims are estimated to be very few, less than 1% from 2010 (5). For the purpose of assessing the use of laboratory tests for the whole primary care, the design was adequate. Some aspects still need discussion concerning the issue of validity. Internal validity is the degree to which the results represent what was intended to be measured, and external validity refers to whether the results can be extrapolated to the entire population. The internal validity will influence the external validity.

**Samples**

The total samples are nearly complete and not a random sample. There is little variation between the two periods, respectively 1 and 3 years, during which we have collected data. This provides a good basis to assume that we have a view of the activity and the external validity is good. The data are collected routinely and not designed for research purposes.

We also made a selection in **Paper II** of children 0–5 years of age. The purpose was to compare the use of CRP at daytime and OOH. To avoid all CRP taken for controls, we decided to use only children, they have high contact rates for acute sickness/respiratory diseases and, as we know from **Paper I,** a high use of CRP. This selection was done to have better internal validity.

Using statistical tests on a population and not a sample of the population is debatable. Although the samples are complete for the selected years, it can also be considered as a sample of many years. Our purpose was to see which variables were independent of each other as predictors of high use of CRP. Multiple regression analyses seemed to be a good model for this purpose and Hosmer and Lemeshow tests also showed good fitting of the model used in **Paper II**.

**Selection bias**

In Study II, the information about the doctors' characteristics was missing for doctors that were not employed as RGPs. This did not affect the results in daytime practice, but at OOH, other doctors sent more than 50% of all claims and that represents a selection bias. In **Paper II** we therefore excluded them from the analyses and only compared the RGPs to avoid this bias.

There were great differences between RGPs in the number of consultations OOH they had per daytime contact, possibly causing less reliable basis for comparison of working style.

**Validity**

Diagnoses validity may be poor in primary care claims (90-92) and the use of general and unspecific diagnoses are increasing in Norway (5). The given diagnosis may be affected by the treatment given; an organ specific diagnosis is more often used if CRP is taken, if CRP is elevated or if there is given a specific treatment as antibiotics (63).

Because of this possible verification bias, the use of diagnoses as explanation for the variation in use of CRP may have limited value. A high degree of general and symptom diagnoses (cough and fever for example) are used and can be considered as being working diagnoses. Most of them will never be reexamined for correctness and one should be cautious of using them as valid explanations for the found variation.

### 9.1.2 Study III (Paper III and Paper IV)

**Design**

We have used a randomized controlled trial and an observational design in these two papers. Randomized controlled trials are the gold standard for testing effect of interventions, as screening. For such studies, it is important to include similar groups and have a random selection and follow-up after to avoid missing and systematic errors. Observational studies have some limitations. It is especially important to avoid biases that interfere with the results.

**Data collection**

The inclusion criteria were intentionally wide to cover most of the diagnoses relevant for the main outcomes: prescription and referral. The investigator or doctor that decided the treatment (outcome) did not influence inclusion and randomization by the nurses. We used systematic allocation; every third included child was randomized to the intervention group. It is possible that there may be a selection bias since we did not observe the randomization. However, we have no reason to believe that the nurses selected sicker children for a CRP test than for the control group. In the control group, we used ordinary treatment; the doctor could order a CRP test as normal, during or after the consultation. All doctors were informed by their leader that there was an ongoing study before it commenced but they were not reminded every day.

We used a questionnaire on paper for the parents before the consultation. It was not previously validated in other studies and designed for only this purpose by the investigators. The parents were asked 10 questions and were supposed to answer with a cross-mark in check boxes in front of different possible answer options. We have used the answer about the duration and their assessment of sickness: seriousness and type of infections (Appendix) in our analyses in the papers. The nurses had a form to fill in with examination results, and they were to ask the parents about different symptoms (yes or no) and the duration of the symptoms (Appendix).

Alere Afinion™ CRP was used at all OOH-services and at the emergency clinic, a rapid in vitro diagnostic test for quantitative determination of C-reactive protein (CRP) in human blood using 1.5 μL capillary bloods.

## Validity

*Internal validity*

Internal validity refers to the extent to which the study results and conclusions are based on the data in the study. Confounders that can affect both exposure and outcome variables will result in lower internal validity. Uncertainty in experiments and investigations is due to errors. Systematic errors are problems or measurable inaccuracies that are consistent and always affect the results in the same direction. Random errors are statistical fluctuations in different directions occurring randomly because of limited precision of the measurement apparatus/devices. A larger number of observations will reduce these errors. Selection bias may be a systematic error in both the inclusion and randomization.

All eligible children were to be included, but at the OOH services, the nurses had this task in addition to their normal job. On busy days, they could not prioritize recruiting children for the study. We still think the inclusion was random with no selection bias of importance. At the emergency clinic, we had a study nurse on randomly selected days and all children these days were included so that no selection bias would be possible. We have no reports about parents who refused to participate in the study so this kind of selection bias was small.

The intervention group and control group were similar to one another with reference to baseline characteristics so we think the randomization was appropriate and without any significant selection bias.

Ideally, in randomized controlled trials the patients and doctors who decide the treatment should be blinded. It was not possible or reasonable in this study to take a blood test of every third child and not analyse it and keep it secret from the parents. The parents' assessment of their child and knowledge of the test result may affect the decision making process, but it is not possible to estimate the impact of these factor on decision-making.

*External validity*

External validity means the extent to which the results can be generalized to the whole population of children in Norway and other countries. The inclusion in the third study was broad and is generalizable to children with fever in a similar primary care population with low prevalence of serious infections.

**Reliability**

The reliability of a test result or measure means that it is identical or similar each time measured.

*The CRP test result*

All OOH-services are member of NOKLUS and follow the programme for internal and external quality control for primary care. At the emergency clinic, we used nurses who also worked OOH and were educated in the same quality programme; they tested the apparatus with internal quality controls every day. Since the same type of test apparatus was used at all clinics, we find the test result to be as reliable as possible.

*The questionnaire*

The questionnaire was paper based and not previously validated. We used check boxes in front of the answers, and most of the questions were descriptive. The parents sometimes marked two answers. We have used three variables from the questionnaire (Figure 9). The first question about days was correctly answered with a number on all forms, but the figures varied greatly; some parents estimated their child's cough had persisted for 30 days – perhaps only because the cough was persistent for what the parents perceived as a long time, and others indicated just a few days for this actual fever episode. Maybe, this question was not clear enough. The variable is not a good measure of the duration of the actual sickness but it reflects the great variation. Some parents contact the first day of acute sickness, others waited or have been to consultation many times before. The question about seriousness was marked with only one answer by all parents, but for the question about sickness, some marked two answers, both bacterial and viral. We then coded them as bacterial even if they had marked both since it reflects that they think about the possibility of bacterial infection.

*The examinations*

The nurses at all OOH services were instructed by the researcher in how to ask the questions and take the measures, either directly at a meeting or indirectly by their leader who had got the information directly. Only experienced nurses working regularly at the services took part in the study. They used their ordinary equipment; measured the temperature with an ear thermometer or a rectal measure for the youngest children as usual, and oxygen saturation using their ordinary pulse oximeter. Only one OOH service was not familiar with the pulse oximeter for children, and they borrowed the probe for children from the researcher. We have no reason to believe that it affected the results; most reports of missing were because children who were uncomfortable with undergoing the examination.

**Figure 9. Three questions from the questionnaire used in the analyses**

***For how many days has your child been ill?***

Number of days _____

***How serious do you consider the health condition of your child?***

☐We think it will heal itself but want a check to be sure

☐The child is so ill, we think medications/inhalations are needed

☐The child is so ill, we think antibiotics are needed

☐The child is so ill, we think hospitalization is necessary

***What sickness do you think that your child has?***

☐A viral infection

☐Bacterial infection with need of antibiotics

☐I don't know

**Sample size**

The power of a study (defined as the probability of rejecting the null hypothesis when it is false) is based on a number of factors but is always dependent on the sample size, the statistical level of significance and the effect size. In our study using a two-sided test, the significance level was set at 5%.

The inclusion was challenging, time-consuming for the OOH services and took longer than expected. The effect size was the difference in prescription rate between the intervention group and the control group. We expected a difference of 40% but it turned out to be only 18%. The sample size needed to reach a significant result with this difference would amount to more than 1500 and that was not possible with this design.

It was not easy to estimate the effect size before the study. Effect size can also be considered as the clinically relevant effect one wishes to consider. In our study, there were three possible results, each of which would have clinical implications. First, a significant reduction in the prescription of antibiotics would be a desired clinical effect, and then we could recommend routinely using this diagnostic test. We know that the test is used extensively already, and we suspect that it causes increased prescribing compared to when it is used at medical indication. A result with a significant increase in prescription would result in a warning against widespread use. The third possible result; a lack of efficacy of screening with CRP (null hypothesis cannot be ruled out) will also provide implications for clinical practice; it should not be necessary to test (or prick) over 50% of all children at OOH services if it is not relevant for the choice of treatment. The effect size that can be regarded as reasonable is debatable, but we believe that even a small significant change is of clinical significance since even a small change means many prescriptions for antibiotics per year. These considerations were the reason why we terminated the study after including 400 children, because inclusion was so slow and time-consuming for the OOH-services. Despite lower power, we thought the matter could shed light on the clinical efficacy that extensive use of CRP tends to have on the choice of treatment in a primary care setting.

**Missing values**

The major problems with a randomized trial generally arise in the period after intervention to follow-up; non-compliance and missing outcome. In our study, the treatment choice was the outcome and it was recorded during the same contact. We did not need a follow-up contact so we had few problems with missing outcomes; only four children had to be excluded because of no outcome variables.

To avoid missing explanatory variables we encouraged the nurses to do some examinations independently of the doctor and to ask some questions about symptoms. This was time-consuming, and we might have included more children if we had just used the medical record, but then we would have had much more missing and not so consistent/substantial data. The main data missing from this part pertained to the variable oxygen saturation because some children were uncomfortable and refused to have the probe on their finger; otherwise, there were very few missing variables.

The medical record is short, and it varies widely from doctor to doctor as to the recorded reasons for contact, sickness and findings. In particular, negative findings are often not recorded at all, but the fact that they are not recorded does not always mean that the findings are negative. The hand-written records from the paediatric emergency clinic were challenging to read but to minimize varying interpretation, the same researcher read all the records. Most missing values were related to inadequate record keeping from the lung and ear examination. We chose to code the record with no information about auscultation or ear examination as missing on these variables. There were few missing data for all variables but in total, as in the multiple regression analyses of predictors for referral, it was summarized to 38%. Moreover, the goodness of fit test (Hoshmer and Lemeshow test) was significant for this analysis, indicating no good fit of the model. We then performed a multiple imputation on all actual variables in the analyses, assuming that all missing data were random in the study.

**Predictor analyses**

Multiple regression analyses were chosen in both studies to find predictors for the categorical dependent out-come variables. First, we analysed all possible variables with bivariate analyses. The significant ones were also checked for possible interactions but no interactions were found. Backward and forward selection methods were also performed, but no differences were found. Temperature, respiratory rate and age were continuous variables and not transformed. Vomiting, earache, use of paracetamol, findings on the auscultation and ear examination were all binary and needed no transformation. For CRP values, we tested different categorization options. Used as a continuous variable it was difficult to compare those that had not taken a CRP from those with low CRP values. We tried different groupings but found no significant differences. CRP not taken was then established as a reference category.

Lower than 20 mg/dl was chosen as the first group because many studies operate with this value as a rule-out value for serious infections (37). Some studies operate with 80 mg/dl as a rule-in value (64). We had few children with values of more than 80 mg/dl, so 60 mg/dl were chosen to get groups that were equal in size. The different cut-off -values did not affect the results. For the other variables with more than two categories, we used the lowest, neutral or normal situation as reference value.

The model was checked using the Hosmer and Lemeshow test. Before imputation in **Paper IV**, we had too many missing for the outcome variable referral, but after the imputation with no deleted cases in the analysis, the model fitted well for this variable as well.

The data were also strictly independent; there were no repeated outcome measures from the same individuals.

## 9.2 Discussion of results

### 9.2.1 Use of laboratory tests out-of-hours

The use of laboratory tests at OOH services in Norway was completely dominated by the use of CRP (**Paper I**). Some reasons are obvious, such as the fact that follow-up by the same doctor is precluded if a test is sent to analysis at an external laboratory. In addition, the fact that only acute conditions should be seen at OOH services explains the higher use during OOH than in the daytime, as we found in **Paper II**. As a marker of acute inflammation, the test is highly relevant for the majority of the conditions at the OOH services: infections, abdominal pain, confusions etc. The apparatus available today for point of care testing has also been quick (response in minutes), reliable and easy to use (requiring only 1 drop capillary blood). There are no equivalent tests on the market. Differential counting of leukocytes requires more expensive equipment (cell counter) and is more time consuming. It has not shown the same ability to detect serious infections; it is best early in the course and is probably rather a complement to CRP where available (37, 93, 94). A use rate of 0.5% found in our study shows clearly that this test is not readily available and little used. Procalcitonin has also been tested as an inflammation marker but not found to be better than CRP, and the test is not available for near patient testing (37, 95). The prevalent and preferred use of CRP can be explained by this.

Use rate of CRP was high, especially for children, and in respiratory diseases and fever. Few earlier studies have reported on this topic in Norway or in other countries having CRP available at OOH services. Two Swedish studies found that GPs used CRP in 36-42% of all consultations pertaining to respiratory infections (65, 96). We found this same level at daytime in **Paper II**. A large randomized trial from Belgium that compared acutely ill children in two groups: CRP on all and CRP restricted to children identified as at clinical risk, found that a CRP in the last group was taken in 20% (97). Compared to this our frequency rate of nearly 60% OOH found in all three studies is surprisingly high.

For all frequently used diagnoses we found a higher level of CRP use during OOH than at daytime (**Paper II**) but also great variance between doctors for the same diagnoses. Diagnoses are poorly validated, so this may be one explanation. At daytime, there may be differences between RGPs in terms of how many children and acute infections they see each day, depending on the list and organization of their practice. At OOH, we would expect more uniform use of CRP, if it were used at strict indications, but here as well we found great variations, suggesting that other, more organizational factors may affect usage.

### 9.2.2 Characteristics of the doctors who order CRP

Some predictors for requesting a CRP were found in all three studies. Characteristics of the doctors, such as age, RGP or not, sex and centrality were found in Study I at OOH services. Young age was a clear predictor, as was being a female doctor. The type of doctor, RGP or not, was not significantly associated. Probably age was a confounder since RGPs are older than ODs. The same was found in **Paper II** with only RGPs at OOH services; young age was strongly associated with high use of CRP. Female RGPs did not take CRP more often than male OOH in **Paper II**. Compared to **Paper I**, this group of female RGPs working OOH is probably more experienced than the female doctors in **Paper I**. At daytime, we found that not being a certified specialist was correlated with high use of CRP and a patient list including a larger number of children was associated with lower use. A Swedish study from 2015 found that in 38% of contacts, the doctor found CRP testing to be crucial to further management. The non-specialist GPs found it significantly more important than the GP specialists (98). All this reflects experience; a young doctor with limited experience with children will probably use more tests to be sure he/she makes the correct decision about treatment.

Another factor to explain the high rate of CRP is the busyness most doctors experience. Working a lot will probably necessitate more efficiency, as well as the fact that many clinics are very busy with a heavy patient flow. The organization model of larger intermunicipal casualty clinics often located in central areas and remuneration of doctors with a fee-for-service system favours seeing many patients in as short a time as reasonably possible. Work is rationalized by having the auxiliary personnel perform a CRP test on all patients with a fever ahead of consultation and have the answer ready for the examining physician. The tendency of more use of CRP in central places from Study I and the correlation between a high number of consultations OOH and high use of CRP test from Study II support this.

Efficient work styles also generate more income for the doctor. We think financial motives may be one reason for the high use of CRP. Our studies do not ask the doctors directly about this topic. An additional qualitative study could have been a better design for supporting this statement. Nevertheless, we believe our results warrant pointing out that the financial incentive may be of importance. An earlier study from Norway has found that this activity based remuneration system affects the attractiveness of the GP profession (6). It has also been found, in Scotland, that the opportunity for young doctors to supplement their income by working OOH does in fact matter (99). That is the same tendency we see here: young doctors with a high working capacity who use the OOH services to increase their income.

It was also clear from the results from Study II that the working style you adopt follows you. The habit of taking many or few CRP tests at daytime was highly associated with the same practice OOH. This was also found in an earlier study from Norway where the conclusion was that practice style reflects a deeply rooted behaviour in terms of how to practise medicine (100). In addition, our results in Study III where we found predictors for ordering a CRP test showed the same tendency. The paediatricians who were not used to having CRP so readily available did not use it more even though they could have had the results in only a few minutes during the period of the study.

### 9.2.3 Prescription of antibiotics to children after screening with CRP

The definition of screening in medicine is: a strategy used in a population to identify an unrecognized disease in individuals without signs or symptoms. We have called this pre-consultation CRP-test “screening” in the heading of this subsection. It is debatable whether a CRP test on all febrile children is a screening since they have some symptoms. However, we know the incidence of serious infections is low and blindly taking a test with low sensitivity and specificity of all children with no symptoms presents the same challenges as screening for other low-prevalent diseases. This is the background for why we use this term in **Paper III**.

The comparison of background variables showed no significant differences between the intervention group and the control group in Study III. Fewer were categorized as “in normal general condition” in the control group but not significantly different (p=0.052). The mean age was 2.3 years, but the median was lower, reflecting the fact that we had more children in the youngest age group. This was expected from what we know about the contact rate to OOH services, with a peak around 1 year (Figure 7). The mean duration was 6.5 days and the median was 4 days. Most parents reported a duration of just a few days but some parents reported up to 30 days of the sickness and the mean then increased. The great variations in duration and symptoms make some comparisons difficult.

A comparison of the background variables between children examined by paediatricians and OOH doctors shows significant differences. At the paediatric emergency clinic, the children did not seem so ill; they had significantly lower temperature, respiratory rate, higher oxygen saturation and fewer were categorized as ill. It is an open clinic, the difference from OOH services is that one does not need to ring to get an appointment and no advice is given from the nurse; the parents themselves decide if they want an appointment. We think that at the other OOH services, some of the healthiest children would have been advised by the nurse, over the telephone, to wait and use symptomatic treatment. This fact may also affect the outcome results, the prescription and referral rate.

The total prescription rate of antibiotics was 23%. Since inclusion was wide, including children with a fever and/or respiratory symptoms, this prescription rate has to be compared with other studies including all children with acute illness in a primary care setting. Prescribing of antibiotics has been much debated in recent years and a decrease has been desired. Recently published studies are therefore more comparable with our study. One comparable Norwegian study found a prescription rate of 26% (67). Sweden is known to have a low total prescription rate (Figure 5). In the study from 2015 (children and adults), the prescription rate was 28% (98) and here otitis media patients were excluded. A recent study from OOH services in the United Kingdom with a sample of 200 children (0-16 years) found the prescription rate to be 30% (64). One from Wales had 26% (63) and two Dutch studies including children 3 months to 6 years of age report a prescription rate of 36% (60) and 37% (61). Our findings correspond well with earlier findings that Norwegian doctors in general are restrictive in prescribing antibiotics compared to the rest of the world.

The effect of the intervention was not significant for any of the two outcome variables. There was an increase in prescription in the intervention group, from 22% in the control group to 26% after CRP pre-consultation testing but not significant. At the emergency clinic, the rate was lower and nearly the same in both groups. Thus the main difference was in the OOH-service group; the increase here was 32% but still not significant. Probably this group was too small to get significant results. However, we believe the results show a clear trend towards increased prescribing and not a decrease as desired, and not serving the purpose for which the test was intended. The paediatricians were not accustomed to having CRP test results so readily available at the clinic and were probably more experienced with severely sick children. This may explain the lack of difference, but the fact that children seemed healthier at this clinic may also explain the low prescription rate in both groups (18 and 19%).

The distribution of different types of antibiotics prescribed was not different between OOH doctors and paediatricians. Phenoxymethylpenicillin (PcV) was prescribed in 67%, amoxicillin in 20% and a macrolide in 9%. Compared to an earlier Norwegian study (67), there has been a reduction in use of macrolides, which is desirable and expected due to the Norwegian Prescription Database (Figure 3 and 4). A Danish study from 2015 found the following distribution for children from their national data: PcV (45%), amoxicillin (34%) and erythromycin (6%) (101). The study from Wales found PcV prescribed in 15%, amoxicillin in 57% and macrolides in 8% (63). Developing countries have a worse distribution. Third generation cephalosporins is reported to be prescribed in 69% of all prescriptions in two children departments in Indian hospitals. The patients were children 0-18 years of age with acute gastroenteritis, respiratory tract infections, enteric fever, viral fever or unspecified fever (102). From primary care or outside hospitals little is published, but studies from China have shown prescription rates of 50-74% in rural areas and a high usage of broad-spectrum antibiotics (103). Compared with other countries, Norwegian physicians prescribe more narrow-spectrum antibiotics.

### 9.2.4 Referral to hospital after screening with CRP

For the second outcome variable, we found a reduction of referrals to hospital in the intervention group, from 9% to 5%, a reduction of 44%. Low number of referred patients in total makes the results less reliable. The reduction was greater at the emergency clinic than at the OOH services. Possibly, a negative / low CRP reassures the parents and doctor if there was uncertainty at the time of decision. On the other hand, the predictor analyses showed no significant association between CRP values and referrals to hospital; therefore, the results are difficult to interpret.

Comparison with studies from elsewhere are challenging because the outcome variable is uncertain. We do not know if the referred children with suspected severe disease actually had a serious illness, or if some of those not referred should indeed have been in hospital; this is a weakness of the study. We should have had access to the hospital records of all to have valid data on this, and follow-up contact with everyone. To suggest anything about the frequency of severe disease from this study is therefore not possible. Likewise, it is impossible to indicate which variables indicate severe disease. Our data primarily provide a basis for drawing a conclusion about what doctors on call perceive as predictive of severe disease in children and the referral decision.

The most comparable study is from the UK primary care with a similar design. Children were randomized to CRP or not CRP and prescription rate and referral rate were measured. It had fewer children, a total of 200, referral rate here was 5.5% and again no significant difference between the groups with CRP or no CRP taken (64). In the Belgian study including more than 3000 children, the referral rates were 2.9% when CRP was taken of all and 2.1% when taken at clinical risk (97), and also here no significant differences were found between the two CRP groups in the trial as in our study. They conclude that there is no reason to test all children with CRP; it should be reserved for children with a higher risk after a clinical assessment. From our study it is not possible to conclude otherwise.

### 9.2.5 Factors predicting antibiotic prescription

Predictor analyses for both outcome variables were performed with the same model and after imputation of missing values in **Paper IV**. For prescription, the imputation affected the results of use of paracetamol and parents' assessment of sickness, which both had some missing data, but otherwise few differences.

*Predictors*

Earache, use of paracetamol and findings on ear examination all probably express signs of otitis media, but there were divergent results between symptoms and finding. Only half of those with signs had earache and only findings at examination were a significant predictor in the multiple analysis. Earache is a symptom that will be difficult for children under 3 years to express. There must therefore be considerable uncertainty associated with this symptom, especially in younger children. The more objective findings on ear examination and whether paracetamol had been used were strongly associated with a prescription. This correlates well with the results from the diagnoses. If otitis media is given as a diagnosis, 2 of 3 got a prescription, even with low CRP values or not taken CRP. Other studies have also found earache as a predictor. From Wales in 2015, signs of ear infection and poor sleep were associated with a prescription (63), and they also found that prescription was more strongly associated to the diagnoses than to findings, although correlated. Two Dutch studies found that being inconsolable or having earache disturbing sleep were associated with a prescription (60, 82). They also found higher age, duration of fever, dyspnoea and ill appearance to be associated, in contrast to our findings. On the other side, vomiting was negatively associated as in our study. Measured temperature gave different results in the mentioned studies and in our study; we did not find it significantly associated. Temperature measured is also an uncertain variable. Some parents give their child paracetamol before the consultation, others probably want to give the doctor the "right impression" of how ill the child is, and do not give anything.

*Rapid Strep A test*

Strep A test for rapid diagnosis of bacterial pharyngitis/tonsillitis with group A streptococci was also available at all OOH services, not at the emergency clinic. The guidelines for use of antibiotics in primary care recommend that this test be positive before giving antibiotics for pharyngitis/tonsillitis. Also viral infections can cause a similar clinical picture as tonsillitis with high CRP values, which is why this test is not recommended to diagnose bacterial tonsillitis (80). In our study 47 subjects were diagnosed with tonsillitis but only three of these had taken the test and all tests were negative. The guidelines seemed not to be followed and the test results seemed to be ignored by the OOH doctors. This was also found in a Finnish study from 2016 including 200 children of whom 38% with no evidence of bacterial infection (positive antigen test or culture) were nevertheless given antibiotics. They also found that CRP tests were not able to distinguish streptococcal from non-streptococcal infections (104).

*CRP value's role*

CRP values more than 20 mg/dl were significantly associated with prescription of antibiotics. The group under 20 mg/dl had the lowest prescription rate and probably represents those in which CRP is used to rule out bacterial infections. The test is then used as a supplement to support the conclusion the doctors have reached by clinical examination; namely, that the child needs no antibiotics. For the groups with values more than 20 the findings were more divergent. For the diagnoses tonsillitis, otitis and pneumonia the prescription rates were high at all values but for the other diagnoses, such as URI, the prescription rate was clearly increasing with increasing CRP values. This is also shown in an earlier study from Sweden. Antibiotics were used more extensively in the treatment of diagnoses indicating bacterial aetiology, irrespective of the outcome of measured CRP, in contrast to ‘viral’ where the prescription rates for antibiotics rose with higher CRP values (65). They also conclude that the test results are not interpreted according to the guidelines. Our guidelines recommend expectance if the CRP value is below 50-100 mg/dl on the second day or later. Based on this, the prescription with low CRP seems high and the guidelines do not appear to be followed. If CRP is taken at indication, it should be expected that it was to use the test as a guideline and to avoid prescription if the result was below the recommended value. The results show rather a general lack of confidence in the CRP test or that the CRP value is considered as a false negative. A third possible explanation is that it may be difficult to deny prescription to the parents when the CRP value is slightly elevated. We must expect that the parents also have some expectations about what will come out of the testing. It is not easy to de-emphasize the test result when the result is already known.

*Parents' assessment*

Parents' assessment was also slightly significantly associated with prescription. If they had chosen bacterial infection instead of or in addition to no opinion or viral infection (some had marked both) on the questionnaire, it was linked with higher prescription. This is also shown in other studies; concerned parents (60) is a factor of significance but it is also shown that clinicians' uncertainty often results in "just in case" prescribing (68, 105). A Danish study from 2016 found a positive relationship between parents' educational level and prescription rate: the lower the number of years of education, the higher the prescription rate (106). A Swedish study of possible explanations for different antibiotic prescription rates in children found no such associations but concluded that the differences may be attributable to different prescription behaviours (107). Strategies to better understand the parents' need and time to explain the rationale behind the decision to prescribe or not prescribe should be emphasized for clinicians working at busy OOH services to reduce the prescription rate.

*How to reduce prescription of antibiotics?*

One major goal is to reduce prescriptions of antibiotics without contributing to increased complications of common infections in children. In Norway we have achieved a low prescription rate in general for all age groups, and CRP testing since the -80s has undoubtedly helped to reduce prescribing somewhat (24, 26, 71, 108-111). It appears, however, that the CRP values are emphasized at lower levels than those recommended in evidence-based guidelines. More extensive testing of all children in a primary care setting with an already low prescribing rate of antibiotics has not been shown to reduce prescription additional, neither in our study nor in other recently published studies (64, 112). To prove that CRP has a further effect on the prescription rate, the recommendations given have to be followed. In our study, the prescription rate would have been 4% if all with CRP values under 60 were not prescribed antibiotics. This is hypothetical but shows the potential that lies in using the test along with a clinical evaluation and following guidelines. It is possible to postpone prescribing where one does not have a clear bacterial cause such as positive strep-A tests and the child's general condition is satisfactory. However, it also requires good information to parents and a good opportunity for follow-up if the condition worsens.

### 9.2.6 Factors predicting referral to hospital

*Limitations*
The second outcome variable, referral to hospital, had different predictors than prescription. Generally, this outcome variable occurred less frequently and our material is small considering that serious bacterial disease rarely occurs in primary care. However, we know that many children are referred to hospital because of uncertainty about the diagnosis and which treatment that is necessary. None of our OOH services was more than 30 minutes driving distance from the hospital. This has probably also affected the result; it is easier to be admitted to hospital for an extra check when it located nearby. With longer distance, the referral rate probably would have been lower with fewer of those "just in case" referrals (113-116). In **Paper IV** we wanted to look for predictors and identify factors that are emphasized by the clinicians when they admit to hospital. It is not possible to make or validate a decision support tool with so few patients participating. We also lack information about all patients after the hospitalization. How many of the referred children were sent straight home again after an assessment and without hospitalization is not

known, nor if any children should have been placed in hospital but instead were sent home after first consultation.

*Respiration*

The main reason for referral to hospital was disturbed respiration. Different factors confirmed this; increased respiratory rate, reduced oxygen saturation and signs of auscultation were all significantly associated. This reflects the diagnoses most often admitted to hospital: pneumonia and asthma/bronchiolitis. Respiratory rate is one of four vital signs. Vital signs are defined as a group of the 4 most important signs that indicate the status of the body's vital (life-sustaining) functions (117). Familiarity with the measurement of vital signs is necessary for all clinicians working with acute illnesses. For children it may be the only sign indicating serious illness during the first hours of the sickness and is therefore especially important. Pulse and blood pressure measurements are not common parameters used in the assessment of sick children. Temperature as the fourth vital sign is not easy to use as a sign; many viral infections also give the same high temperature at the start of the infections. In our study, it was not significantly associated with referral. We also registered other red flag symptoms such as peripheral capillary perfusion, but no children were found to have reduced circulation in our study.

*CRP value's role*

CRP values were not significantly associated with referral in our study, although some of the highest CRP values were found in children that were admitted. It may be that our sample was too small to show any significant associations. This reflects that the respiratory symptoms are predominant, and the CRP values do not seem to affect the doctors in their decision of refer or not. A Dutch study from 2013 validated a clinical prediction model for assessing the risk of serious infections in children with fever in emergency departments (118). They also found that tachypnea and oxygen saturation < 94% were important predictors for pneumonia and other serious infections. Reduced oxygen saturation and chest wall retraction were useful to rule out other serious infections and elevated CRP values predicted both pneumonia and other serious infections.

*Parents' assessment*

The parents' assessment of referral is strongly associated with the referral rate. Nearly all (6 of 7) children where the parents expected referral were admitted to hospital. This indicates that parental concerns are of significance and are taken into consideration. In addition, it probably means that parents are their children's closest guardians and are probably best to assess the child's general condition. It can also be difficult for the clinicians to deny referral when the parents expect it or want it. He may find it unnecessary, but it is easier to admit than to discuss and argue with the parents. None of these considerations can be assessed in more detail from our study. What is known is that, in addition to the clinical examination results, a form of "gut feeling" exists that can affect the suspicion of serious infection and referral to hospital. It is defined as an instinctive response by clinicians to the concerns of the parents and the appearance of the child. A Belgian study from 2012 investigated this using children in primary care. They found that acting on gut feeling has the potential to significantly reduce the number of missed cases without causing an unmanageable number of false alarms (85).

*Urine dipstick tests*

Urine analyses with the dipstick test were done in only 3 cases presenting with fever. Two of them had pyuria and also elevated CRP values and were admitted to hospital. The third had a normal urine-dipstick test and CRP. Urine analyses are important to detect urinary tract infections and especially together with CRP testing to find pyelonephritis in children. It should be on the repertoire at all OOH services is probably underused in the assessment of children with fever.

# 10. Conclusions

**Main conclusions of this thesis**

- The point-of-care CRP test is the most widely used test in Norwegian OOH services, especially in children and for respiratory illnesses. Younger doctors with less experience use it more frequently than older doctors. Doctors working at centrally located OOH use it more frequently than doctors working in more rural areas.
- The point-of-care CRP test is frequently used throughout primary care. All investigated RGPs use it more in the OOH services than in daytime practices. The most frequent users at daytime are the most frequent users at OOH. Young RGPs with a high number of consultations have significantly higher use of CRP in OOH services. The differences in use of CRP between doctors cannot be explained by the spectrum of diagnoses.
- CRP is used extensively in children presenting to OOH services with fever or respiratory symptoms, especially when the child has high fever and if the parents suspect a serious infection.
- Pre-consultation screening with CRP does not significantly affect the prescription of antibiotics or referral to hospital.
- Main predictors for prescription of antibiotics are CRP values > 20 mg/L, use of paracetamol during the past 24 hours and signs on ear examination. Vomiting is negatively associated. Disturbed respiration is significantly associated with hospital referrals. Parents' assessments of sickness and seriousness are also significantly associated with outcomes.

# 11. Implications and recommendations for future research

## 11.1 Clinical implications

This thesis sheds light on diagnostics in Norwegian OOH services, describes how the CRP test is used and how it affects the diagnosis of acutely ill children. It seems clear that not only clinical conditions affect the use of CRP. Also, organizational factors affect the frequency. We have shown that pre-consultation use of CRP in children does not reduce prescription of antibiotics. This could lead to the following clinical implications:

- Extensive testing with CRP outside clinical indication in a population with a low prevalence of serious infections can result in multiple false positive tests. This can lead to unnecessary prescription of antibiotics. Low CRP values may represent a false sense of security if the child's clinical condition is not applied as the basis for the testing. All CRP testing should therefore be performed only when clinically indicated.
- Clinical assessment of a child's respiration is the main factor in the assessment of acute sick child with fever and respiratory symptoms. Everyone who works in primary care with acutely ill children must have knowledge about this when prioritizing waiting-time and otherwise give the right treatment at the right level. Nurses also should be given adequate training in assessment of sick children.
- OOH services must be organized so that there is enough time spent on the assessment of sick children and that a committed effort is made to ensure good information to the parents about the condition and the treatment choices one makes.

## 11.2 Future research

CRP testing has probably been a contributing factor in keeping the prescription rate of antibiotics low in Norway but more testing will not reduce prescriptions further. Therefore, other contributing factors must be considered. Future research should emphasize the following topics:

- Studies in primary care in countries with a low prescription rate to investigate the factors that can reduce the use of antibiotics further.
- What factors influence the doctor in the decision making process when communicating with parents?
- What information is most important to provide when meeting uncertain or concerned parents with sick children to safeguard them in parenting?
- Development and validation of a clinical prediction model that includes clinical symptoms, signs and laboratory testing for use in primary care.

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## Appendix

**Spørjeskjema til foreldre på legevakta**.
*Kryss av eitt eller fleire kryss for det som høver best*.
***1. Kor mange dagar er det sidan barnet ditt begynte med symptom på sjukdom?***

Antal dagar _____
***2. Har du/de forsøkt å kontakte fastlege med dette problemet?***

☐Ja ☐Nei
Hvis ja:
☐Kom ikkje gjennom på telefon
☐Ringte men kontoret var stengt
☐Ringte men ingen ledig time
☐Ringte men vart bedt om å oppsøke legevakt
☐Har vore til konsultasjon hjå fastlege, men oppsøker legevakt pga. forverring
☐Anna________________________
Hvis Nei:
☐Akutt forverring av tilstanden
☐Tør ikkje vente lengre med å gå til lege
☐Passer best å gå til lege utanom arbeidstid
☐Kjem aldri gjennom på telefon til fastlege
☐Får aldri time til akutte tilstander på dagtid hjå fastlege
☐Anna________________________
***3. Kor alvorleg vurderer du/de sjølv tilstanden til barnet ditt?***

☐Trur det vil gå over av seg sjølv men ønskjer legesjekk for å vere sikker
☐Barnet er så dårleg at vi er usikre på om det treng behandling
☐Barnet er så dårleg at vi lurer på om det treng antibiotika
☐Barnet er så dårleg at vi trur det er behov for innlegging i sjukehus
***4. Kva sjukdom trur du/de barnet ditt har?***

☐Virusinfeksjon
☐Bakteriell infeksjon med behov for antibiotika
☐Har ingen bestemt formeining
***5. Bruker barnet fast eitt eller fleire av følgjande medikament?***

☐Ventoline
☐Flutide
☐Andre________________________
***6. Har du/de søkt informasjon om tilstanden i forkant?***

☐Spurt familie, venner eller barnehagepersonell om råd
☐Søkt informasjon på internett
☐Ringt fastlegekontor eller legevaktsentral for råd
***7. Kva undersøkingar trur du/de må til for å finne ut kor alvorleg tilstanden er?***

☐Undersøking av lege
☐Blodprøver

☐Vidare undersøkingar på sjukehus

***8. Har barnet tidlegare fått tatt CRP-prøve (stikk i fingeren)?***

☐Ja ☐Nei ☐Veit ikkje

Hvis ja, kva erfaring har de med prøvetaking frå tidlegare?

☐Ukomplisert å stikke barnet

☐Smertefullt men gjekk raskt over

☐Barnet opplevde prøvetakinga som traumatisk og vegrer seg når vi oppsøker lege igjen

Hvis ja, kva erfaring har de med resultatet på prøven?

☐Prøven hadde ingen betydning, legen vurderte ikkje svaret

☐Prøvesvaret hadde liten betydning for val av behandling

☐Prøvesvaret fekk avgjerande betydning for val av behandling til barnet

☐Prøvesvaret gjorde oss tryggare på at diagnose og behandling var korrekt

Nummer:_________

## Questionnaire to parents at out-of-hours emergency clinics.

*Mark with x for the answer you think is most correct*.

***1. In how many days your child has been ill?***

Number of day's _____

***2. Have you tried to contact your regular doctor/GP?***

☐Yes ☐No

If yes:

☐Nobody answered the telephone

☐The medical office was locked

☐They had no free appointment for us

☐Called them, but get advice to contact an emergency clinic out-of-hour

☐Have been to a doctor but the health condition is worse

☐Other reasons______________________

If no:

☐Acute worsening of the condition

☐It cannot wait until next day

☐It is best to go to doctors in the evening

☐I don't have a regular doctor/GP

☐I never get an appointment for acute conditions with my regular doctor/GP

☐Other reason______________________

***3. How serious you consider the health condition to your child?***

☐I think it will heal itself but want a check to be sure

☐The child is so ill; we think it's necessary with medications/inhalations

☐The child is so ill, we think it needs antibiotics

☐The child is so ill, we think it needs hospitalization

***4. What sickness do you think that your child has?***

☐A viral infection
☐Bacterial infection with need of antibiotics
☐I don't know

***5. Does your child use any of these medicines regularly?***

☐Ventoline
☐Flutide
☐Other_______________________

***6. Have you tried to get information about the sickness from other?***

☐Asked family members, friends or the staff in the kindergarten for advice
☐Information at internet
☐Called the medical office or out-of-hours central for advice

***7. What kind of examinations you think has to be done to find out how serious it is?***

☐Examination by a doctor
☐Blood tests
☐Hospitalization

***8. Have your child taken a CRP-test before (a blood test in the finger)***

☐Yes ☐No ☐Don't know
If yes, what is your experience with the test?
☐Uncomplicated
☐Painful but not long-lasting
☐The child found it traumatic and don't want to go to medical offices any more
If yes, what is your experience with the test results?
☐The test result had no meaning; the doctor didn't consider it
☐The test result was of little meaning to the choice of treatment
☐The test result was of vital importance
☐The test result ensured us that the diagnosis and treatment was correct

| **Nummer:** | | | | | | |
|---|---|---|---|---|---|---|
| Alder | Mnd/år | | | | | |
| Kjønn | Gutt | | Jente | | | |
| Kronisk sykdom | Astma | | Allergi | | Anna | |
| Oppkast/brekninger siste døgnet | Ja | | Nei | | | |
| Allmenntilstand | Upåverka | | Lett nedsatt | | Svært nedsatt/litekontaktbar | |
| Feber siste døgnet | Ja | | Nei | | | |
| Døgnvariasjon feber | Ja | | Nei | | | |
| Hudutslett | Ja | | Nei | | Antall dgr | |
| Øyreverk | Ja | | Nei | | Antall dgr | |
| Hoste | Ja | | Nei | | Antall dgr | |
| Tungpustet | Ja | | Nei | | Antall dgr | |
| Sår hals | Ja | | Nei | | Antall dgr | |
| Diarè | Ja | | Nei | | Antall dgr | |
| Redusert diurese | Ja | | Nei | | Antall dgr | |
| Nakkestivhet | Ja | | Nei | | | |
| Brukt paracetamol siste døgn | Ja | | Nei | | Antall | |
| Brukt Ibux siste søgn | Ja | | Nei | | Antall | |
| Temperatur konsultasjonstidpkt | grader | | | | | |
| Kapillær fylningstid | >3 sek | | <3 sek | | | |
| Hydreringsgrad | Nedsatt hudturgor | | Tørre slimhinner | | Normal | |
| Respirasjonsfrekven | per/min | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| s | | | | | | |
| Oksygenmetning (pulsoxymeter) | <90 | | 90-95 | | >95 | |
| Puls (fra pulsoksymeter) | | | | | | |
| CRP (kvart tredje barn) | | | | | | |

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# Use of laboratory tests in out-of-hours services in Norway

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**ORIGINAL ARTICLE**

# Use of laboratory tests in out-of-hours services in Norway

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**Abstract**

*Objective.* To investigate the use of laboratory tests and which factors influence the use in Norwegian out-of-hours (OOH) services. *Design.* Cross-sectional observational study. *Setting.* Out-of-hours services in Norway. *Subjects.* All electronic reimbursement claims from doctors at OOH services in Norway in 2007. *Main outcome measures.* Number of contacts and laboratory tests in relation to patients' and doctors' characteristics. *Results.* 1 323 281 consultations and home visits were reported. Laboratory tests were used in 31% of the contacts. C-reactive protein (CRP) was the most common test (27% of all contacts), especially in respiratory illness (55%) and infants (44%). Electrocardiogram and rapid strep A test were used in 4% of the contacts. Young doctors, female doctors, and doctors in central areas used laboratory tests more often. *Conclusion.* CRP is extensively used in OOH services, especially by young and inexperienced doctors, and in central areas. Further investigations are required to see if this extensive use of CRP is of importance for correct diagnosis and treatment.

**Key Words:** *Clinical chemistry tests, CRP, diagnostic tests, emergency medical services, primary health care*

## Introduction

In Norway every municipality is responsible for the emergency primary health care for their inhabitants and visitors, both during office hours and out-of-hours (OOH). OOH work is with few exceptions compulsory for regular general practitioners (RGPs), but because the duty comes in addition to ordinary work it is often seen as a burden. At least half of the OOH consultations are done by other doctors (ODs) than RGPs [1–3]. The majority of RGPs are qualified specialists in general practice. The ODs may be newly qualified doctors serving a compulsory practice period, or temporary employed doctors who work in the daytime in hospitals or universities. In many rural districts doctors are working at OOH alone from their daytime surgeries, while larger districts usually run casualty clinics staffed with nurses in addition to the doctors. Many municipalities have now organised OOH services as larger inter-municipality cooperatives, and in some cities there are specialized emergency clinics with direct access [4,5].

Generally, the OOH services are well equipped with laboratory and diagnostic instruments. In a previous study we found that all OOH services have at least six point-of-care laboratory tests available. These were C-reactive protein (CRP), haemoglobin, glucose, urine analysis, u-HCG pregnancy test, and rapid Strep A test [6]. Laboratory tests are used in approximately 30% of the OOH consultations [3].

The use of point-of-care testing in primary care has increased for the purpose of reducing the time taken to make decisions on patient management. Thus, the availability of a limited number of laboratory tests is especially welcome for OOH services, with its high patient turnover. Infections and inflammatory conditions are prevalent among patients using OOH services, but with the low prevalence of serious bacterial infections it is challenging to discriminate them from self-limiting illness. CRP is the dominating inflammation marker available at every OOH service while just a few OOH services have cell counters [6].

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A few point-of-care laboratory tests are available for diagnostic use in out-of-hours services in Norway.

- A laboratory test was taken in 31% of all consultations/home calls.
- C-reactive protein (CRP) was the dominating test (27% of all contacts), and the rate was especially high in small children.
- Test use was most frequent in out-of-hours services in central areas and by younger doctors.

The aim of the present study was to investigate to what extent laboratory tests are used in OOH services in Norway, and how factors like patients' and doctors' characteristics, diagnostic groups, and geography may influence their use. We wanted especially to analyse the usage pattern of the CRP test, which is the most frequently used test.

## Material and methods

The material comprises all electronic compensation claims from identified doctors working in OOH services in Norway in 2007. The claims are sent to the Norwegian Health Economics Administration (HELFO) which is responsible for remuneration.

The claims are usually electronically transferred to HELFO, but in 2007 a small proportion were still sent on paper (not included in our material). In 2006 it was estimated that paper-based claims accounted for 4.9% of all contacts with the OOH services [7]. At some OOH services the doctors have a fixed salary, and the compensation claims are registered for the OOH service/municipality, and not for an identified doctor. Some simple consultations are paid in full by the patients, and may not be registered by HELFO if there are no extra fees like fee for laboratory tests or procedures. The extent of underreporting has been estimated at 8% of consultations and home visits in the age group 12 + and almost nothing for younger children because of full reimbursement of all costs [3,7].

We received an anonymous data file from HELFO with the following variables: patient's sex, age, centrality of the municipality, diagnosis, doctor's age, sex, and type (RGP or OD), and the specific fees that were claimed. The centrality is defined as a municipality's geographical location in relation to a centre where there are important functions (central functions) and is measured on a scale of 0–3 where 0 is the least and 3 is the most central [8].

Every claim contains a fee indicating the type of contact (e.g. home visit or consultation in surgery/casualty clinic) and various fees for different procedures. There is one basic fee for all laboratory tests; in addition there are specific fees for different laboratory tests done at the service, except for haemoglobin, sedimentation rate, and urine analysis. All contacts are coded with ICPC2 diagnoses (International Classification for Primary Care).

HELFO and the Privacy Ombudsman for Research (Norwegian social scientific data services) assessed the project. As it is not possible to identify individuals in this material, directly or indirectly, the project was not subject to obligatory notification. The data were analysed in SPSS 18.0 with simple frequencies analysis and cross-tables. In order to evaluate the significance of different doctors' characteristics a binary logistic regression analysis was performed. The use of a laboratory test (the basic lab fee) per contact for each doctor was used as a dependent variable (dichotomized by the median value 0.2756) and the doctor's age (dichotomized by the median value 38), sex, type of doctor (RGP vs. OD), and centrality (0/1 vs. 2/3) as independent variables to calculate odds ratios with 95% confidence intervals.

## Results

The material consisted of 1 240 235 claims for consultations and 83 046 for home visits. RGPs sent 47% of the claims while other doctors sent 53%. Mean age for RGPs was 44 years, for other doctors 38. Female physicians were younger than male physicians (37 vs. 42 years) and sent 22% of the claims.

The age distribution of the patients is shown in Figure 1, revealing a peak of contacts for the age group 0–1 year, and a smaller peak around age 20. There were only minor differences in distribution of contacts by gender.

### *Laboratory/diagnostic tests*

Fees for laboratory or diagnostic tests were found in 31% of the contacts (consultations and home visits). The distribution of laboratory claims by age was similar to the distribution of contacts (Figure 1). The absolute numbers of various tests and rates per 1000 contacts are given in Table I.

Simple frequency analyses of test use indicated that younger doctors tend to use laboratory tests more often than older doctors (Table II). Similar analyses also indicated that RGPs make less use of laboratory tests than other doctors, but this difference disappeared in the multiple regression analysis. Tests were used significantly more by doctors in central OOH services, and slightly more by female doctors (Table III).

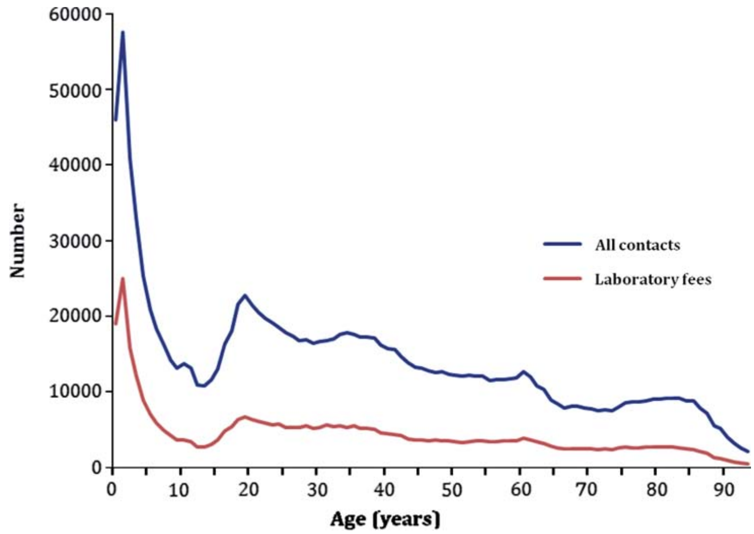

Figure 1. Distribution of all contacts and laboratory fees by age.

*Use of CRP*

Respiratory disorders were the most frequent ICPC-2 diagnoses used (24% of all contacts), and CRP was taken in 55% of these contacts. For age group 0–1 years 42% of the contacts included a CRP test and for age group 2–6 years 34%. For older patients 23–26% of the contacts included a CRP test. There was slightly less use of CRP in the most rural municipalities (24%) compared with more central municipalities (28%), with largest difference in the youngest group (36% vs. 44%).

Home visits were more frequent in the most rural districts compared with more central areas (11% vs. 5%). With increasing centrality the rate of CRP use

Table I. Total numbers of various laboratory tests and numbers per 1000 out-of-hours contacts (n = 1 323 281 consultations or home visits).

| Laboratory test | n | Per 1000 contacts |
|---|---|---|
| Any laboratory test | 411 170 | 311 |
| C-reactive protein (CRP) | 361 905 | 273 |
| Electrocardiogram | 55 527 | 42 |
| Rapid strep A test | 53 524 | 40 |
| Glucose | 24 741 | 19 |
| Secondary test to external laboratory | 16 242 | 14 |
| Pregnancy test (urine HCG) | 9212 | 7 |
| Haematological analysis with blood counter | 6256 | 5 |
| Mononucleosis test | 5323 | 4 |
| Urine culture | 3981 | 3 |
| Faecal occult blood test | 2396 | 2 |
| Incubated urine sample to external laboratory | 1940 | 2 |
| Cholesterol, potassium, creatinine, GGT, ALAT | 1418 | 1 |
| Prothrombin time (INR) | 1411 | 1 |
| Microalbuminuria | 864 | < 1 |
| Chlamydia test | 822 | < 1 |
| Glycated haemoglobin (HbA1c) | 527 | < 1 |
| Microscopic examination of preparation | 91 | < 1 |
| Trichomonas in vaginal secretion | 91 | < 1 |
| Test for scabies or fungus | 75 | < 1 |
| Helicobacter pylori test | 64 | < 1 |
| Immune fluorescein test for herpes virus | 41 | < 1 |
| Glucose tolerance test | 29 | < 1 |
| Manual colouring and examination of blood smear | 27 | < 1 |

Table II. Use of various laboratory tests according to doctors' sex and age: Numbers per 1000 out-of-hours contacts (n = 928 169 by male doctors and n = 268 861 by female doctors).

| | Basic fee | | CRP | | Strep A test | | U-HCG | | Glucose | | ECG | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age group | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| < 31 | 330 | 350 | 300 | 330 | 30 | 45 | 9 | 9 | 24 | 22 | 50 | 46 |
| 31–39 | 310 | 330 | 270 | 300 | 40 | 40 | 7 | 11 | 18 | 24 | 45 | 43 |
| 40–49 | 320 | 300 | 270 | 250 | 46 | 45 | 6 | 6 | 21 | 15 | 38 | 35 |
| > 49 | 264 | 269 | 235 | 232 | 40 | 48 | 4 | 6 | 13 | 16 | 34 | 30 |
| Total | 310 | 320 | 270 | 290 | 40 | 44 | 6 | 9 | 20 | 20 | 42 | 41 |



per 1000 home visits were 76, 56, 55, and 28. CRP use was most frequent during home visits in the age group 0–6 years (130 per 1000 contacts), 59 in age group 7–20, 37 in age group 21–60, and 44 in age group > 60. There were no significant differences for CRP use during home visits by doctors' age, sex, or type.

## Discussion

The data on which this study is based are comprehensive and almost complete. The differences shown are therefore real and not in need of significance testing. However, the use of fees may not always reflect practice. Some doctors may forget to claim fees they are entitled to. On the other hand, economic motives may cause doctors to order more tests than clinically indicated or even claim fees for tests not performed. We have no reason to believe that this is a common occurrence.

There were significant age differences between different types of doctors. RGPs were older than other doctors, and male doctors were older than female doctors. This age difference is a confounder that has to be taken into account when interpreting the found differences in ordering tests. The bivariate difference between RGPs and OD disappeared in the multiple regression analysis, and is explained by the age difference in the groups. However, the other differences like age, centrality, and sex remained significant even after controlling for other variables.

Table III. Odds ratio for using laboratory tests: Use of basic lab fee per contact, dichotomized by median value (0.2756) (3802 doctors were included in the analysis).

| | Odds ratio | 95% confidence interval |
|---|---|---|
| Old vs. young doctor[1] | 0.53 | 0.46–0.62 |
| Female vs. male doctor | 1.23 | 1.07–1.42 |
| RGP vs. other doctor | 0.99 | 0.86–1.15 |
| Central vs. rural OOH service[2] | 1.98 | 1.72–2.27 |

Notes: [1]Dichotomized by median age (38). [2]Central is two highest centrality categories, rural two lowest.

Since a separate fee does not cover measurement of haemoglobin, sedimentation rate, and urine analysis, we do not know how frequently these tests are used or combined with other laboratory tests. Many tests (e.g. glycated haemoglobin, HbA1c) have little relevance in OOH settings and are therefore rarely used. Earlier we have found that only 13% of all OOH services have a cell counter [7]. Since it is used in only 0.5% of all contacts, it seems that few OOH services find it to be a valuable supplement to CRP. However, this may be different in other countries that have a stronger tradition of using white blood cell indicators. A comprehensive review has shown that white blood cell indicators are less valuable than inflammatory markers for ruling in serious infection, and have no value in ruling out serious infection [18].

Centralization to larger OOH services has reduced the number of home visits. Usually, patients are transported to the OOH service where a wider repertory of diagnostic equipment and laboratory tests are available. In smaller, rural OOH services the workload is less, and it is easier for the doctor to do home visits and also bring diagnostic equipment with him/her. This is reflected in a higher rate of home visits and CRP tests per home visits in these areas.

We are not aware of earlier studies on the frequency of laboratory tests in OOH services. Some have reported on the use of CRP in general practice, for different diagnostic groups, and related to antibiotic prescription for respiratory infections. Two Swedish primary care studies found that CRP was performed in 42% and 36% of patients with a respiratory diagnosis [15,16]. A possible explanation for the higher number in our material (55%) may be that many doctors at OOH services are more inexperienced than RGPs. In 2006 Norwegian RGPs did 88% of the consultations in the daytime, but at OOH services they did only 47% of the consultations [7]. In addition there might be more severe acute infections at OOH services than at daytime RGP practices.

The organization at central OOH services probably explains the significantly higher use of laboratory tests here. With ancillary staff it is easier to order laboratory analyses, and it may even be a routine to measure CRP in every febrile child.

CRP is being used as a universal test for bacterial infections in many organ systems, not only respiratory disorders. Many studies have tried to find a cut-off value for bacterial infections but still there is no conclusion [18,19]. CRP testing may be used as a kind of reassurance, but its utility has been questioned as a diagnostic and prognostic marker for serious bacterial infections. In small children it is of limited value alone as an indicator of serious illness, especially during the first 12 hours of sickness [11–13,17–19]. Also the test is painful and gives the child an unpleasant experience of the doctor's consultation. In any case, it is important that CRP is interpreted in relation to clinical findings.

Most studies of children and markers for bacterial infection are done at hospital/emergency departments where the prevalence of serious infections is higher than in primary care. Considering this and the low prevalence in primary care, the rate of CRP use among children seems unnecessarily high here. These findings probably also apply to primary care outside Norway.

In conclusion, CRP is by far the most frequent laboratory test in OOH services. It is most often used in respiratory illnesses and in small children. Older doctors use laboratory tests less frequently than younger doctors, probably reflecting different clinical experience. Centralization of OOH services results in higher use of laboratory tests. Further investigations are required to study the clinical relevance of this extensive use of CRP in primary care.

## Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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BMC Family Practice

RESEARCH ARTICLE Open Access

# Point-of-care testing with CRP in primary care: a registry-based observational study from Norway

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## Abstract

**Background:** Norwegian primary health care is maintained on the regular general practitioners (RGPs), GP's contracted to the municipalities in a list patient system, working at daytime and at out-of-hours services (OOH services). Respiratory disease is most prevalent during OOH services, and in more than 50 % of the consultations, a CRP test is performed. Children in particular have a high consultation rate, and the CRP test is frequently conducted, but the contributing factors behind its frequent use are not known. This study compares the RGPs rate of CRP use at daytime and OOH in consultations with children and how this rate is influenced by characteristics of the RGPs.

**Methods:** A cross-sectional register study was conducted based on all ($N = 2\ 552\ 600$) electronic compensation claims from consultations with children ≤ 5 year during the period 2009–2011 from primary health care. Consultation rates and CRP use were estimated and analysed using descriptive methods. Being among the 20 % of RGPs with the highest rate of CRP use at daytime or OOH was an outcome measure in regression analyses using RGP-, and RGP list characteristics as explanatory variables.

**Results:** One third of all RGPs work regularly in OOH services, and they use CRP 1.42 times more frequently in consultations with children in OOH services than in daytime services even when the distribution of diagnosis according to ICPC-2 chapters is similar. Not being approved specialist, have a large number at their patient-lists but relatively few children on their list and a large number of consultations with children were significantly associated with frequent use of CRP in daytime services. The predictors for frequent CRP use in OOH services were being a young doctor, having many consultations with children during OOH and a frequent use of CRP in daytime services.

**Conclusions:** The increase in the frequency of CRP test use from daytime to OOH occurs in general for RGPs and for all most used diagnoses. The RGPs who use the CRP test most frequently in their daytime practice have the highest rate of CRP in OOH services.

**Keyword:** Point-of-care CRP testing, Primary care, GPs working-style, Children

## Background

Primary health care in Norway is based on regular general practitioners (RGPs) with daytime practice contracted to the municipalities in a list patient system and are also supposed to take care of acute medical problems at daytime. The municipalities are also responsible for organizing an out-of-hours service (OOH service) which can be contacted by all inhabitants 24/7 when RGPs are not available, in afternoons, nights and holidays. When accessibility to RGPs is low, the use of OOH services increase [1]. The OOH organization varies from a single doctor on call in smaller municipalities to larger units serving more municipalities or the larger cities, with doctors and other healthcare professionals working together in casualty clinics [2]. The RGPs are obliged to take part in the OOH service and have approximately 50 per cent of all out-of-hours contacts; the rest are covered by physicians temporarily working in primary care as locums or residents or by

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hospital doctors. Only a small proportion (24 %) of the OOH doctors have finished a 5-year training program and are approved specialists in general practice [3, 4]. It has previously been shown that the RGPs working in OOH services have shorter consultations and request less laboratory analyses than do other doctors [5].

Norway has a high rate of contacts to the OOH services because of the gate-keeper function for secondary care, in contrast to other countries, where the patients can choose between emergency departments and OOH services [6–9]. The majority of contacts are related to infections and respiratory sickness (75 %), especially in the youngest age group and during the winter months [10]. Data recorded at 7 different OOH services in 2007 estimating national figures on use-pattern showed that 76 % of all contacts were considered as not urgent in a strict medical sense [11]. Small children (0–5 years) have an especially high contact rate (430/1000 inhabitants per year) [12] and infectious diseases dominate both the use of OOH services and the RGPs in daytime practice [13]. This patient group may therefore be appropriate to study how the use of CRP varies among RGPs in daytime practice and OOH services.

On-site measurement of C-reactive protein (CRP) is the most frequently used laboratory test in Norwegian OOH services [12]. The test aims at differentiating bacterial infections from viral/less severe infections, and after its introduction as a point-of-care test, it has been widely used in Norway: at 35 % of all consultations at OOH-services [10]. Compared to most other countries the CRP test is used clearly more frequent in Norway and reasons for such variations should be assessed, especially since the benefit of using the test has been discussed [14–16]. Different factors seem to influence use of the test: the age, gender and experience of the doctor, as well as the geographical centrality and organization of the OOH service [12]. The wide differences in use indicate that factors other than sickness or symptoms in the population may contribute to the variation. Economic incentive may be a factor, since the doctor is paid extra for conducting a CRP test. For OOH services, the municipalities most often cover the costs while the doctors keep the income. During daytime service, the RGPs most often cover the costs of services and retain the income from their own surgery practice, and thus the economic incentive per test is relatively low.

It is not known if the usage pattern of laboratory tests at OOH reflects the individual RGP's overall working style or if it represents a change associated with working for the OOH services. When the RGPs work with their own patients at daytime, they have a different age mix, different list length, and are located in either rural or urban districts, which may affect the patients' encounters with their RGPs [17]. In the OOH services, the RGPs meet a random group of patients. Difference in use from daytime to OOH can be explained with different prevalence of serious illness and different ways of organizing services, but there should in theory be no difference in the use of CRP between RGPs at OOH services if the use is based strictly on medical indications.

The aim of this study is therefore threefold: (1) to assess the use of CRP tests in consultations with children 0–5 years, (2) to compare the use of CRP in regular daytime practice and OOH services, and (3) to study associations between variations in the use of CRP and characteristics of the RGPs.

## Methods

The study is a cross-sectional, register-based, nationwide study in primary care in Norway. The material comprises all claims from consultations with children aged 0–5 years from RGPs' daytime practice and from OOH services in 2009, 2010 and 2011.

Both the daytime RGP practices and OOH services are mainly financed by a fee-for-service system. The RGPs send a claim to the Norwegian Health Economics Administration (HELFO) for each patient contact, with information about the RGP's identity, type of contact, daytime or OOH and eventually fees for laboratory tests or procedures. The claim also includes information about age and gender of the patient and a diagnosis based on ICPC-2 [18–20]. The term diagnoses in the Norwegian ICPC-2 are used for both symptoms/complaints and diseases like infections or injuries.

The fee for a consultation increases by approximately one third (NOK 92, i.e. approximately 12 Euros) when taking a CRP test, compared to a consultation without a laboratory test.

The HELFO data have been linked with information from the national RGP database that includes information about the individual RGP's age, gender, speciality, list size, whether the list is open for new patients, and practice municipality.

The total material of 2 552 600 contacts with children aged 0–5 years formed the basis for describing the use of CRP in consultations. When comparing the RPGs' practice in daytime and OOH, we included only the group of RGPs that had more than a total of 20 consultations by children 0–5 years during the three-year period of daytime service, and that also worked OOH during the same years and had more than a total of 20 OOH consultations with children ($N = 1931$). The RGP database has no information about doctors working as locums and residents in daytime practice or OOH services, therefore not included in all analyses.

### Ethical approvals

HELFO and The Norwegian Data Protection Authority allowed the use and linkage of data. The Norwegian Directorate of Health, as register owner, also approves the linkage of registers.

### Statistics

The data were analysed in IBM SPSS 21.0 using descriptive analyses, T-tests and regression analyses. To illustrate the distribution of mean CRP rates per RGP at daytime and OOH we used quintiles and cross tabulation. Being in the fifth quintile with the highest rate of CRP use daytime and OOH, respectively, was used as an outcome variable in the multivariable logistic regression models. Goodness-of-fit of the model was assessed by a Hosmer and Lemeshow test for different cut-off-values of the dependent variable but showed no differences if we used fourth and fifth quintile together or just fifth quintile, so the fifth quintile was chosen. The $p$-value in the test was 0.417 for a high CRP use at daytime and 0.474 for a high CRP use at OOH, assessing good fitness of the model chosen.

Explanatory variables in the multivariable logistic regression analyse were age, gender, specialist status of the RGP, total number of contacts daytime and OOH, CRP used per contact at daytime, size of patient list, whether the list was open and number of children in the list. They are chosen to test different theories of possible association using available relevant data in register and the full model is presented.

## Results

Table 1 shows the number of consultations and use of CRP by RGPs and other doctors in daytime and OOH services. CRP was used in 31 % of all consultations at daytime and in 44 % of all at OOH, and to a higher extent by doctors that were not RGPs (53 % at OOH). When selecting the 20 most used diagnoses, we found that respiratory diseases, infections and fever constituted 50 % and 59 % of all contacts at daytime and OOH, respectively, and a CRP test was used in 44 % and 58 % of the consultations. These 20 diagnoses represented 81 % of all CRP tests and the mean CRP rates for the RGPs with these diagnoses are shown in Table 2, all rates significant higher OOH compared to daytime.

Table 3 compares the RGPs working both in daytime practice and OOH services with RGPs working in daytime practice only. The RGPs working both places were younger, fewer were approved specialists in general practice, they were more often males and had fewer patients at their list. However, the use of CRP was not significant different.

The distribution of diagnoses at ICPC chapter level at daytime and OOH was rather similar (Fig. 1). The CRP rate was significant higher at OOH than at daytime in the total material, mean difference from daytime to OOH 0.14 (CI 0.09-0.19, $p < 0.001$) (not tabled).

### RGPs' use of CRP

Table 4 shows the variation in the rate of CRP usage per RGP, distributed in quintiles. The accuracy for being in the same group in daytime and OOH services, if we accept a variance of one quintile, is 91.9 %. If the diagonal is considered as a strict constraint, 42.1 % of the doctors are in the same quintile for both daytime and OOH. The proportions over and under the diagonal are almost identical (28.8 % vs 29.0 %). Only a small minority (4.3 %) of the doctors with the highest rate of CRP at the OOH services had a low rate of CRP at daytime. Similarly, we found that only 2.9 % of the RGPs were both high users at daytime and in the lowest quintile at OOH. The 207 doctors (10.7 %) in the fifth quintile both at daytime and OOH used 23.0 % of all CRP tests at OOH and 18.0 % of all tests at daytime.

### Predictors for high usage of CRP tests

A multiple regression analysis was performed in order to identify associations between characteristics of RGPs and a high CRP rate. We analysed predictors for being in the highest quintile of CRP use at daytime and OOH

**Table 1** Distribution of all consultations in the regular general practice scheme with children 0–5 years at daytime and at out-of-hour services, and rate of CRP use during 2009–2011

| | Total | RGPs also working OOH | RGPs not working OOH | Other doctors[a] |
|---|---|---|---|---|
| Consultations | | | | |
| Daytime (n) | 2 080 743 | 758 709 | 977 235 | 344 799 |
| Daytime, distribution (%) | 100 | 36 | 47 | 17 |
| OOH (n) | 471 857 | 251 246 | 0 | 220 611 |
| OOH, distribution (%) | 100 | 53 | 0 | 47 |
| Rate of CRP use in Consultations | | | | |
| Daytime | 0.31 | 0.30 | 0.29 | 0.33 |
| OOH | 0.44 | 0.43 | 0 | 0.46 |

[a]Other doctors are locums, residents etc

**Table 2** Distribution of mean CRP rate per diagnose for the regular general practitioners, the 20 most used diagnoses

| Diagnoses | CRP rate daytime (SD)[a] | CRP rate OOH (SD)[a] | *P*-value |
|---|---|---|---|
| Fever | 0.76 (0.20) | 0.82 (0.22) | <0.001 |
| Respiratory infection | 0.70 (0.23) | 0.82 (0.22) | <0.001 |
| Pneumonia | 0.75 (0.26) | 0.88 (0.22) | <0.001 |
| Influenza | 0.74 (0.26) | 0.86 (0.22) | <0.001 |
| Bronchitis/bronchiolitis | 0.69 (0.25) | 0.82 (0.24) | <0.001 |
| Acute upper respiratory infection | 0.60 (0.23) | 0.72 (0.26) | <0.001 |
| Acute tonsillitis | 0.70 (0.28) | 0.78 (0.28) | <0.001 |
| Viral infection | 0.72 (0.25) | 0.82 (0.25) | <0.001 |
| Throat symptoms | 0.69 (0.26) | 0.84 (0.24) | <0.001 |
| Streptococcal infection | 0.70 (0.28) | 0.78 (0.28) | <0.001 |
| Cough | 0.52 (0.24) | 0.74 (0.27) | <0.001 |
| Acute laryngitis | 0.64 (0.29) | 0.69 (0.29) | 0.001 |
| Gastroenteritis | 0.60 (0.28) | 0.74 (0.28) | <0.001 |
| Vomiting | 0.62 (0.28) | 0.78 (0.25) | <0.001 |
| Diarrhoea | 0.49 (0.27) | 0.81 (0.26) | <0.001 |
| Conjunctivitis | 0.14 (0.14) | 0.28 (0.26) | <0.001 |
| Otitis media | 0.39 (0.25) | 0.59 (0.31) | <0.001 |
| Abdominal pain | 0.41 (0.25) | 0.78 (0.25) | <0.001 |
| Asthma | 0.41 (0.25) | 0.78 (0.25) | <0.001 |
| Urinary infection | 0.79 (0.29) | 0.94 (0.11) | <0.001 |

[a]*SD* Standard deviation

independently (Table 5). A high rate of CRP at daytime was associated with not approved RGPs, female RGPs, a larger list size, fewer children at list and a large number of consultations with children. We found that a high frequency rate of CRP at daytime was strongly associated with the same tendency at OOH. In addition, being a young doctor and having a large number of consultations with children were factors that were significantly associated with a high rate of CRP in OOH services.

## Discussion

### Main findings

This study from Norwegian primary care shows that 82 % of all consultations with children 0–5 years are at daytime and 18 % at OOH. Infectious diseases constitute 50 % of consultations in daytime practice and 59 % in OOH practice. CRP is used in 31 % of all consultations at daytime and in 44 % in OOH. RGPs not approved as specialists in general practice, female RGPs and larger list size are associated with more frequent use of CRP in daytime practice. The rate of RGPs' use of CRP in daytime practice seems to be an important predictor for the use of CRP in OOH services.

### Strengths and limitations

This material is comprehensive and is based on three successive years; all electronic claims from RGPs and OOH services are included. The paper based claims that

**Table 3** The study sample of regular general practitioners (RGPs) working also in out-of-hours (OOH) services[a] compared with RPGs not working OOH in 2009–2011 (T-independent sample test)

| Variable | RGP working OOH | RPG not working OOH | *P*-value |
|---|---|---|---|
| Number of RGPs | 1931 | 2834 | |
| RGP mean age, years | 43 | 52 | <0.001 |
| Proportion male RGP (%) | 67 | 64 | 0.005 |
| Proportion approved specialist in general practice (%) | 50 | 62 | <0.001 |
| Mean list size | 1119 | 1231 | <0.001 |
| Mean number of consultations with children 0–5 years in the study period | 391 | 345 | <0.001 |
| CRP rate per consultation at daytime (Standard deviation) | 0.30 (0.13) | 0.29 (0.14) | 0.151 |

[a]Inclusion criteria: RGPs having >20 consultations with children 0–5 years OOH in the period

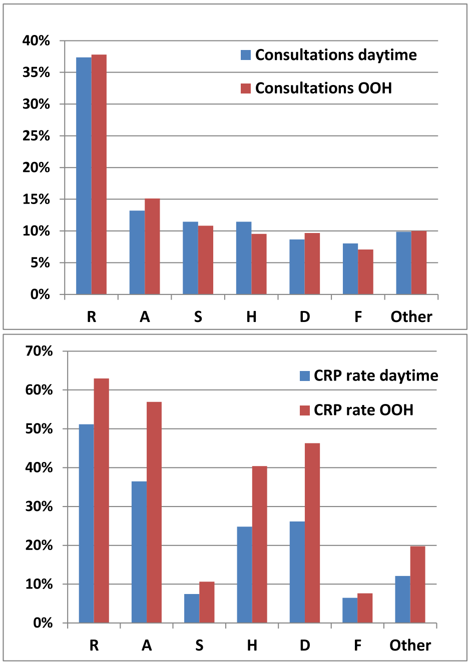


**Fig. 1** Distribution of all consultations and the frequency of CRP use per consultation with children 0-5 years in 2009-2011. The distribution is shown in percentage according to ICPC-2 chapters at the regular GP services at daytime (*n* = 2 080 743) and at out-of-hour services (*n* = 471 857). R: Respiratory, A: General and unspecified, S: Skin, H: Ear, D: Digestive, F: Eye, Other: All other diagnostic groups

are not included are estimated to be 2 per cent in 2009 and less than 1 per cent from 2010 [10], selection bias is therefore minimal, and the results can be seen as representative for Norwegian general practice.

Children under 6 years of age are a homogenous group of patients with a high contact rate with both RGPs and OOH services. The distribution of diagnoses was similar at daytime and OOH, according to the diagnose chapters in ICPC-2. Children seldom have chronic diseases, but some planned controls for asthma and other diseases may explain some more consultations at daytime not taking a CRP. Still we find the reasons for contact at daytime and OOH are comparable, thereby enabling a comparison of RGPs work daytime and OOH.

A limitation is that the validity of diagnoses used in RGP claims is not known. The RGPs may give a more severe diagnosis when the CRP is high. Because of this verification bias the diagnoses should not be used as an explanation for variation in CRP.

Another limitation is that there are rather few consultations and CRP tests included for some RGPs who work less frequently in OOH services. The great difference between the number of consultations at daytime and OOH results in a less reliable basis for comparison. We also have no information about the doctors working as locums in the registry; however as a group they work a lot in OOH services and use more CRP.

Because doctors are paid extra for performing CRP tests, that may be an incentive for taking CRP. The difference between daytime practice and OOH services is that the doctors are not responsible for the actual cost of the CRP test at most OOH services. However, this may vary and our data has no information about which RGPs must cover the cost for the CRP test kit, and this lack of information can be considered a limitation.

In 2009, the contact rate for respiratory infections was especially high, probably due to the swine influenza pandemic during that year, but the increase was equally distributed between the RGPs at daytime and OOH [21].

## Comparison with existing literature

### *Use of CRP*

During the past decade, there has been increased awareness regarding the problem of antibiotic resistance and the high level of prescriptions in primary care for self-

**Table 4** Number of regular general practitioners (RGPs)[a] in the study sample (*n* = 1931) distributed in quintiles by their mean use of CRP per out-of-hours (OOH) and daytime consultations

| CRP rates at daytime (quintiles and rate intervals) | | CRP rates at OOH (quintiles and rate intervals) | | | | | All |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | |
| | | <0.25 (0.18) | 0.25 – 0.36 (0.31) | 0.36–0.45 (0.41) | 0.45–0.54 (0.50) | >0.54 (0.62) | |
| 1 | < 0.18 (0.13) | 234 | 92 | 43 | 24 | 9 | 402 |
| 2 | 0.18 – 0.25 (0.22) | 97 | 133 | 81 | 48 | 25 | 384 |
| 3 | 0.25 – 0.32 (0.29) | 39 | 88 | 122 | 91 | 42 | 382 |
| 4 | 0.32 – 0.41 (0.37) | 13 | 50 | 99 | 117 | 102 | 381 |
| 5 | > 0.41 (0.47) | 9 | 21 | 40 | 105 | 207 | 382 |
| All | | 392 | 384 | 385 | 385 | 385 | 1931 |

Frequency rates are shown as mean number of CRP tests per consultation. Median value in ()
[a]RGPs having >20 consultations with children 0–5 years OOH in the period

**Table 5** Associations between frequent use[1] of CRP in daytime and out-of-hours (OOH) consultations with children (0–5 years) and characteristics of the regular general practitioners (RGPs), lists and practice ($n$ = 1931 RGPs)

| | Predictors at daytime | | | Predictors at OOH | | |
|---|---|---|---|---|---|---|
| Variables | OR[a] | 95 % CI[b] | P | OR[a] | 95 % CI[b] | P |
| RGPs age (per year) | 1.008 | 0.990–1.026 | 0.398 | 0.957 | 0.937–0.978 | 0.000 |
| Female RGP[c] | 1.437 | 1.023–2.018 | 0.037 | 1.134 | 0.776–1.657 | 0.516 |
| Specialist in general practice[d] | 0.700 | 0.507–0.967 | 0.031 | 0.915 | 0.641–1.307 | 0.626 |
| Number of consultations at daytime, children 0–5 years (per 10 contact) | 1.012 | 1.004–1.019 | 0.002 | 0.990 | 0.981–0.999 | 0.028 |
| Number of consultations at OOH, children 0–5 years (per 10 contact) | 1.002 | 0.990–1.014 | 0.723 | 1.026 | 1.013–1.040 | 0.000 |
| List size (per 100) | 1.111 | 1.054–1.170 | 0.000 | 1.016 | 0.958–1.079 | 0.592 |
| Number of children 0–5 years on patient list (per child) | 0.987 | 0.982–0.993 | 0.000 | 1.001 | 0.996–1.007 | 0.599 |
| Closed patient list (yes/no)[e] | 0.841 | 0.627–1.128 | 0.248 | 1.010 | 0.723–1.410 | 0.954 |
| OOH consultations/daytime consultations (%) | 1.001 | 0.997–1.005 | 0.682 | 0.998 | 0.994–1.003 | 0.492 |
| CRP rate daytime (%) | | | | 1.119 | 1.101–1.137 | 0.000 |

1) Frequent use defined as being among the RGP with a CRP rate in the highest quintile in daytime practice and OOH respectively, see Table 3
[a]OR: Odds Ratio
[b]CI: confidence interval
[c]Male RGP is reference
[d]Not approved specialist is reference
[e]Open list is reference
Continuous variables: Age, contacts, number on patient list, rates in percent

limiting infections. Diagnostic uncertainty is a major problem, and the CRP used as a point-of-care test has shown reduced antibiotic prescription in some studies [22–27]. Studies from Sweden have shown that CRP was used in 36–42 % of respiratory infections in 2005 [15, 28] and that is the same level we found at daytime services in our study. However, at OOH we found the usage rate of CRP to be almost 60 % for respiratory infections. There are no studies that make a conclusion of cut-off values for CRP level and when antibiotics are recommended [15, 16].

***RGP's experience***

Two thirds of all RGPs had no contacts with OOH or so few that they cannot be considered to have regular duties in OOH services [29]. To be a young RGP was correlated with a high use of CRP in OOH, and to not be an approved specialist was correlated with high use in daytime service. We think that this reflects the fact that experience is an important factor in the diagnostic process; older doctors are more often specialists, and they use CRP to a lesser extent. A patient list including a larger number of children was associated with a lower rate of CRP and may also be explained by the RGPs having a greater degree of experience with paediatric problems.

***Economy***

A high total number of patients and a high rate of daytime contacts with children indicate a doctor working a lot, having longer days and/or more days with patient contact per week. Financial motivation may be relevant, but another explanation may be that an effective working method is to perform the laboratory test as a routine before the consultation and thereby avoid having to wait for the lab results after the consultation. Among RGPs who work regularly in OOH services, there seems to be a small group of doctors working a lot; these are younger RGPs, but their lists of patients do not exceed a mean of 1200 patients. It probably reflects a group of young doctors with a high working capacity and use OOH-services to increase their income [30]. Having many consultations OOH was also significantly associated with frequent use of CRP and may indicate that the financial motivation matter.

**Implication for practice**

The use of CRP especially in OOH services is high and may reflect an acquired practice to routinely perform a CRP test when the patient has fever or an infection. Studies have shown that CRP may have an effect at reducing prescription when a lower respiratory infection is suspected [22] and since the diagnoses are given at the end of the consultation when the result is ready and the decision of treatment is taken, this may reflect the high level of CRP for diagnoses as fever, cough, respiratory infections, pneumonia, influenza, bronchiolitis and upper respiratory infections. For other diagnoses as sore throat, tonsillitis and otitis the test are known to be of little value [31], still the use in Norway is high. There exist no guidelines in Norway for when the CRP-test is indicated. The guidelines for antibiotic treatments in primary care [32] give some advice for what level of CRP to suspect bacterial infections in lower respiratory infections but for throat symptoms the guidelines recommend a strep A test, so according to this there seem to be an overconsumption of CRP.

There seems to be different factors that can explain the increase in CRP use in Norway. We have mentioned the financial motivation and the doctor's experience, but it must also be taken into account that the organization of the services may play a role. During recent years, OOH services are increasingly organized in larger districts, with many patients treated at short time and only one or very few doctors, assisted by ancillary staff who routinely may take the tests before the consultation. There is a risk involved in placing one's trust in the test alone, for both parents and health personnel, when used to this degree.

An earlier study has shown that RGPs do not change practice style when moving to a new patient population [33]. The strong association between the RGPs' use of CRP in daytime and OOH indicates that they use CRP to an extent that is more a kind of working style for many doctors rather than as a test that is medically indicated.

Our study indicate that to increase the awareness concerning the medical indications for taking laboratory tests is recommended to prevent excessive use. Removal of the financial incentive may reduce the use, but more studies are needed to find more correct medical indications for taking CRP in children and are important for preventing overconsumption.

### Further research

This study does not give any information on the usefulness of the CRP in selecting the best treatment for patients or reducing the use of antibiotics. In further studies, focus should be on clinical findings and treatment, to ascertain whether the use of a CRP test results in less or more use of antibiotics. The clinical significance of CRP in primary care needs to be further investigated.

## Conclusions

The point-of-care test CRP is frequently used all over in primary care and all doctors use it more in the OOH-services than in daytime practice. The RGPs that most frequently use CRP tests in daytime service do the same in OOH services. Being a young doctor and having a high number of consultations result in significantly higher use of CRP in OOH services. The differences between the RGPs use of CRP in OOH services cannot be explained by different diagnoses.

#### Abbreviations

CRP: C reactive protein; GP: General practitioner; RGP: Regular general practitioner; OOH: Out-of-hours.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

IR: Involved in statistical analysis and interpretation of the data, drafting the manuscript and given final approval to the version to be published. ØH: Involved in conception and design of the study, acquisition of data, revising the manuscript and given final approval to the version to be published. SG: Involved in conception and design of the study, acquisition of data and given final approval to the version. SH: Involved in conception and design of the study, revising the manuscript and given final approval to the version to be published.

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III

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# Out-of-hours antibiotic prescription after screening with C reactive protein: a randomised controlled study

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## ABSTRACT

**Objective:** To evaluate the effect of preconsultation C reactive protein (CRP) screening on antibiotic prescribing and referral to hospital in Norwegian primary care settings with low prevalence of serious infections.
**Design:** Randomised controlled observational study at out-of-hours services in Norway.
**Setting:** Primary care.
**Participants:** 401 children (0–6 years) with fever and/or respiratory symptoms were recruited from 5 different out-of-hours services (including 1 paediatric emergency clinic) in 2013–2015.
**Intervention:** Data were collected from questionnaires and clinical examination results. Every third child was randomised to a CRP test before the consultation; for the rest, the doctor ordered a CRP test if considered necessary.
**Outcome measures:** Main outcome variables were prescription of antibiotics and referral to hospital.
**Results:** In the group pretested with CRP, the antibiotic prescription rate was 26%, compared with 22% in the control group. In the group pretested with CRP, 5% were admitted to hospital, compared with 9% in the control group. These differences were not statistically significant. The main predictors for ordering a CRP test were parents' assessment of seriousness of the illness and the child's temperature. Paediatricians ordered CRP tests less frequently than did other doctors (9% vs 56%, p<0.001).
**Conclusions:** Preconsultation screening with CRP of children presenting to out-of-hours services with fever and/or respiratory symptoms does not significantly affect the prescription of antibiotics or referral to hospital.
**Trial registration number:** NCT02496559; Results.


## Strengths and limitations of this study

- The study is a randomised controlled trial evaluating the effect on antibiotic prescription and hospital referral by screening children with fever and/or respiratory symptoms with a C reactive protein (CRP) test before the consultation.
- Nearly complete data since we used dedicated nurses to collect clinical symptoms and findings on all children.
- The study was underpowered, that is, the differences were too small to reach statistical significance.
- Identified predictors of CRP testing are observational and not a result of the randomised trial.

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## INTRODUCTION

Fever, respiratory symptoms and infections are common among children in primary care, especially at out-of-hours (OOH) services.[1] Serious infections have low prevalence in primary care, and even more so after introduction of vaccines for *Haemophilus influenzae* type B and pneumococcal conjugate vaccines.[2 3] It is challenging for clinicians to distinguish serious and low-prevalent diseases from common, self-limiting infections. A severity-of-illness scoring system does not exist for primary care.

In Norway, 85% of antibiotics are prescribed in primary care.[4] Despite a decrease in serious infections, the use of antibiotics has been increasing until 2012, and is generally believed to be unnecessarily widespread.[5] Although there has been an increase in methicillin-resistant *Staphylococcus aureus* (MRSA), the prevalence of antibiotic resistant bacteria is lower than in most other countries.[6] In order to keep the antimicrobial resistance low, it is important to avoid unnecessary antibiotics and use narrow spectrum penicillin when possible.[7]

C reactive protein (CRP) is an inflammation marker, reflecting the severity of inflammation and tissue injury, which is used as a tool to differentiate between bacterial and viral infections.[8] It has high popularity in Norwegian primary care as a point-of-care test, and in OOH services it is used in more than half of all children with respiratory symptoms.[1 9] It thus seems that CRP testing is more like a routine, rather than a supplement to history taking and clinical examination.

The CRP test's role in ruling out or ruling in serious infections, and the cut-off value for when to prescribe antibiotics, have been widely discussed.[8 10] The impact of CRP as a way of reducing the number of antibiotic prescriptions is at best unclear.[11–16]

The aim of the present study was to evaluate the effect of preconsultation screening with CRP on antibiotic prescribing and referral to hospital for children aged 0–6 years presenting at OOH services with fever and/or respiratory symptoms.

## METHOD

We designed a randomised controlled observational study including children aged 0–6 years with fever or any respiratory symptoms. The data consist of clinical symptoms and signs collected by a nurse at the OOH services before the doctor's consultation, a questionnaire filled in by the parents before the consultation, and the medical record. Every third child was randomised to a CRP test before the consultation with a predefined mark in their study folder. The remaining 2/3 received usual care, allowing the doctor to order a CRP test on individual indication. Other tests also available were rapid strep test, urine dipstick test, haemoglobin and glucose.

### Inclusion and procedures

The inclusion of participants took place during the winter seasons from January 2013 to May 2015 at four different OOH services near Bergen and at one paediatric emergency clinic at Haukeland University Hospital in Bergen. This emergency clinic is a walk-in, open access facility, and it is located at a hospital and staffed by paediatricians.

The nurses at the OOH services were trained in the study inclusion criteria and examination procedures. At the paediatric emergency clinic, two trained nurses were engaged specially for the project. The parents were approached by the nurse and invited to participate in the study and fill out a questionnaire prior to the consultation. The nurse did a clinical examination of all children and a CRP test of every child randomised to the test. The CRP result followed the patient to the consultation but not the study folder with the results from the questionnaire. The diagnosis and treatment were recorded from the medical record after the consultation. Numbers of potential patients not asked or approached were not recorded.

### Variables

The two main outcome variables were antibiotic prescription and referral to hospital. Recorded variables from the medical history were age, gender, previous chronic disease, duration of present illness, fever during the past 24 h, variation in fever, vomiting, earache, coughing, dyspnoea, throat symptoms, diarrhoea, reduced diuresis, cervical rigidity, skin rash and use of paracetamol or ibuprofen during the past 24 h. The parents' assessment of the illness and its seriousness was also recorded. Variables from the nurse's examination were temperature, respiratory rate, oxygen saturation, degree of hydration, capillary refill time and general condition on a three-point scale (normal, ill and severely ill). Finally, we recorded whether the doctor was a paediatrician or working at the OOH services.

### Study sample calculation

A power calculation was based on the following presumptions: we presumed that 35% of all children would receive antibiotic treatment based on data from earlier studies,[17 18] and that CRP would be requested in every second consultation.[1] Furthermore, we presumed that the doctor requested a CRP for the most seriously ill children and that 50% of these children would receive antibiotics, compared with 20% for the healthier non-tested group. The null hypothesis was that pretested CRP would not change the frequency of antibiotic treatment, that is, 35% of both groups would receive antibiotics. If a 40% change (effect size) in antibiotic treatment due to pretested CRP was defined as significant, using a two-sided test, power 80%, $\alpha$ level 5%, the sample sizes would have to be 130+259. If effect size was reduced from 40% to 20%, the sample sizes would have to be 525+1050. As it turned out, recruiting participants was challenging, and an interim analysis was performed when 400 children were included. The difference in antibiotic prescriptions was much smaller than what we considered clinically significant, and we therefore decided to stop further recruitment of participants.

### Statistical analysis

Proportions were compared by $\chi^2$ tests, means by Student's t tests. A logistic regression analysis was performed to analyse predictors for ordering a CRP. Explanatory variables that were significant in bivariate analyses were included in the final model. The significance level was set at 5% ($p<0.05$). Data were analysed using IBM SPSS (V.21).

## RESULTS

A total of 401 children were included in the study, but four left the clinic before the doctor's consultation, leaving 397 for inclusion in our analyses (figure 1). A comparison of the two randomised groups is shown in table 1. The mean age was 2.3 years, and 223 (55.6%) were boys. The mean duration of illness was 6.5 days and the mean temperature at the consultation was 38.0°C. No significant differences were found, except that the general condition was more often assessed as normal in the group randomised to a CRP test. A similar comparison of children attending OOH services and the hospital clinic showed that those at the hospital clinic had a significantly lower temperature, respiratory rate, higher oxygen saturation, reported less use of paracetamol, and were assessed to be in better general condition than those at the OOH services (table 1).

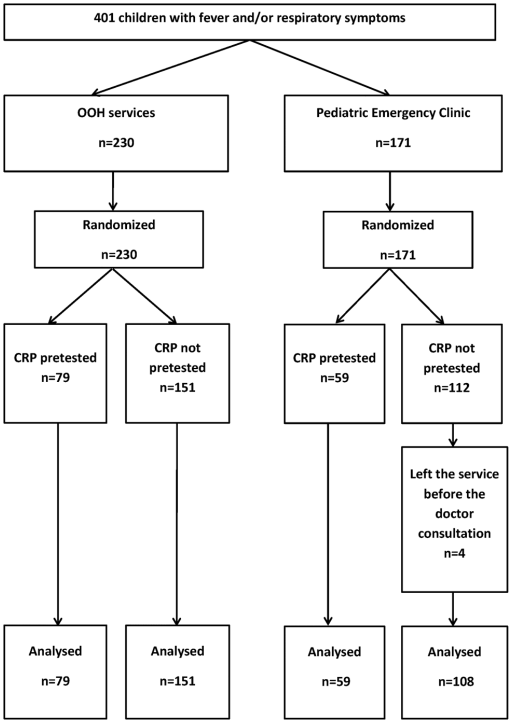


**Figure 1** Flow chart over included and investigated patients in the study. CRP, C reactive protein; OOH, out-of-hours.

A rapid strep test was taken in seven cases; all were negative, but three of the children got a prescription of antibiotics. A urine dipstick test was performed in three cases and two of the children were diagnosed with pyelonephritis.

In total, 93 (23%) received a prescription for antibiotics and 31 (8%) were admitted to hospital. In the group pretested with CRP, the antibiotic prescription rate was 26%, compared with 22% in the control group. In the group pretested with CRP; 5% were admitted to hospital, compared with 9% in the control group (table 2).

The mean result of pretested CRP was significantly lower than when requested by the doctor (21 vs 34 mg/L, p=0.006). Paediatricians ordered CRP tests less frequently than did other doctors (9% vs 56%, p<0.001).

In the logistic regression analyses, three variables remained significantly associated with ordering a CRP test. Use of CRP increased if the parents thought their child had a serious infection or if the child had a high temperature at the consultation. Use of CRP decreased if the doctor was a paediatrician (table 3).

Upper respiratory infection was the most frequently used diagnosis, followed by otitis media and tonsillitis (table 4). Antibiotic prescription rate was highest with tonsillitis (68%) and otitis media/pneumonia (67%). All patients with pneumonia not given antibiotics were referred to hospital (33%). Pyelonephritis, dehydration, bronchiolitis and fever of unknown origin were the other most frequent reasons for referral to hospital.

## DISCUSSION

### Summary

In this randomised controlled study of preconsultation CRP testing of children with fever and/or respiratory symptoms, no significant effect was found on antibiotic prescription or hospital admittance. The study confirms that CRP tests are widely used in OOH services and the excessive use rather tends to increase the antibiotic prescription than to reduce it. High fever and concerned parents predict CRP testing. Paediatricians order CRP testing less frequently than do OOH doctors.

### Strengths and limitations

Our data, according to protocol, are nearly complete due to the effort of the nurses. Collecting data from the medical record only would have been simpler and maybe increased the number of included children, but would probably have caused more missing data.

The inclusion was challenging since the nurses at the OOH services had to ask and inform the parents to participate, interview them and do some tests before the consultation, all this on top of their normal job. The study inclusion may have been given a lower priority on busy days. At the paediatric emergency clinic, we used a dedicated study nurse who was able to include all children for whom the parents consented.

The children who are seen by a paediatrician at the paediatric emergency clinic are unselected and not referred from primary care. At the OOH services, the doctor is a general practitioner (GP), a GP in training or locums. We have no detailed information about the experience of these OOH doctors but know that younger doctors are working more often OOH and use more CRP.[9, 19] How the experience affects the prescription is not known. The paediatric emergency clinic had the function as an OOH service for children in Bergen city, but the children at the clinic seemed to be slightly healthier, maybe due to the walk-in, open access facility. At the other OOH services, the parents had to call first for advice and only got an appointment if the child was assessed to need a doctor consultation.[20] This difference may have influenced the use of CRP tests and prescription of antibiotics. Doctors at the OOH services get an extra fee for each CRP test, while there is no such economic incentive at the paediatric emergency clinic. This may explain some of the difference in use of CRP tests.

The study was not blinded and knowledge about the purpose of the study may have influenced the doctor's prescription pattern. However, this influence would probably affect both groups equally.

One main limitation is the study sample, which was estimated from an expectation that preconsultation CRP

**Table 1** Comparison of background variables in the two randomised groups and the two different clinical settings

| Variables | Intervention group: Pretested CRP n=138 | Intervention group: CRP not pretested n=259 | p Value* | Clinical setting: OOH service n=230 | Clinical setting: Paediatric emergency clinic n=167 | p Value† |
|---|---|---|---|---|---|---|
| Age (year) | | | | | | |
| Mean (SD) | 2.13 (1.7) | 2.44 (1.9) | 0.104 | 2.38 (1.7) | 2.29 (1.9) | 0.638 |
| Median (IQR) | 1.5 (0.9–2.9) | 1.9 (1.0–3.5) | | 1.9 (1.0–3.5) | 1.5 (0.9–3.0) | |
| Duration illness (day) | | | | | | |
| Mean (SD) | 7.0 (11.0) | 6.4 (7.7) | 0.434 | 6.0 (7.7) | 7.2 (9.9) | 0.175 |
| Median (IQR) | 4 (3–7) | 4 (2–7) | | 4 (2–7) | 4 (2–7) | |
| Temperature (°C) | | | | | | |
| Mean (SD) | 38.0 (0.9) | 37.9 (1.0) | 0.893 | 38.2 (0.9) | 37.7 (1.0) | **<0.001** |
| Median (IQR) | 38.0 (37.3–38.7) | 37.9 (37.2–38.8) | | 38.1 (37.5–39.0) | 37.4 (36.9–38.4) | |
| Respiratory rate (breath/min) | | | | | | |
| Mean (SD) | 34.2 (15.0) | 31.8 (12.7) | 0.118 | 34.0 (13.4) | 30.9 (13.6) | **0.028** |
| Median (IQR) | 30 (20–42) | 28 (20–40) | | 31 (22–44) | 25 (20–38) | |
| Earache | 24.4 | 27.4 | 0.566 | 26.3 | 26.3 | 0.955 |
| Cough | 86.1 | 84.0 | 0.665 | 85.1 | 84.8 | 0.987 |
| Dyspnoea | 61.6 | 54.4 | 0.098 | 60.0 | 52.6 | 0.090 |
| Diarrhoea | 19.1 | 18.6 | 0.657 | 18.9 | 18.7 | 0.963 |
| Taken paracetamol during the past 24 h | 65.9 | 66.5 | 0.783 | 73.4 | 57.3 | **0.001** |
| Gender (male) | 53.6 | 56.7 | 0.502 | 57.8 | 52.6 | 0.370 |
| General condition | | | | | | |
| Normal | 29.0 | 20.1 | 0.052 | 18.3 | 29.2 | **0.003** |
| Ill | 68.8 | 76.8 | | 77.8 | 69.6 | |
| Severely ill | 2.2 | 2.7 | | 3.5 | 1.2 | |
| Pulse oximetry | | | | | | |
| >95% | 53.6 | 58.7 | 0.181 | 51.7 | 63.2 | **0.002** |
| 90–95% | 29.0 | 24.3 | | 30.0 | 20.5 | |
| <90% | 2.9 | 1.9 | | 3.5 | 0.6 | |
| Earlier experienced CRP | | | | | | |
| Yes | 69.6 | 71.5 | 0.800 | 76.9 | 63.2 | 0.109 |
| No | 2.2 | 1.5 | | 0.9 | 2.9 | |
| Do not know | 18.8 | 20.2 | | 22.3 | 22.2 | |
| Chronic disease | | | | | | |
| No disease | 75.4 | 74.1 | 0.851 | 74.3 | 74.3 | 0.948 |
| Asthma | 18.1 | 20.8 | | 21.3 | 18.1 | |
| Allergy/other | 6.5 | 5.0 | | 4.4 | 7.6 | |
| Consultation with paediatrician | 42.8 | 42.6 | 0.840 | 0.0 | 100.0 | |

Numbers are proportions (%) otherwise stated.
*p Values from comparison of means and proportions in the intervention groups, using Student's t tests and non-parametric tests.
†p Values from comparison of means and proportions in the different clinical settings, using Student's t tests and non-parametric tests.
CRP, C reactive protein; OOH, out-of-hours.

screening would affect antibiotic prescription to a larger degree than what turned out to be true. If the differences found were to be statistically significant, the study sample would have to be several times larger. The number of referrals to hospital was small in this study and it is not possible to state from these data if screening with CRP affects it. Other laboratory tests (rapid strep test and urine dipstick) were used little.

## Comparison with the existing literature

Children with fever and/or respiratory symptoms are frequent attenders at OOH services, but to compare the distribution of diagnoses is difficult because of the different diagnostic criteria and different precision level. In our material, there were a lot of symptom diagnoses, such as fever, cough, viral illness, upper respiratory infection, etc. This reflects how difficult it is to give a valid diagnosis in primary care. A high CRP result may indicate a more severe diagnosis, such as pneumonia, but rarely these diagnoses are validated in other ways (X-rays, sputum samples, etc).

In one study from general practice in the UK, including children aged <5 years with acute illness,[21] lower respiratory infections were more common, and tonsillitis and ear infections less common than in our study. The antibiotic prescription rate was higher for all diagnoses,

**Table 2** Effect of preconsultation screening with CRP on the rate of antibiotic prescription and referral to hospital

| Variables | Intervention group CRP pretested | | No intervention CRP at request | | p Value |
|---|---|---|---|---|---|
| | Number of patients | Percentage (95% CI) | Number of patients | Percentage (95% CI) | |
| All children n=397 | n=138 | | n=259 | | |
| Prescription of antibiotics | 36 | 26 (19 to 34) | 57 | 22 (17 to 27) | 0.361 |
| Referral to hospital | 7 | 5 (1 to 9) | 24 | 9 (6 to 13) | 0.138 |
| OOH services n=230 | n=79 | | n=151 | | |
| Prescription of antibiotics | 25 | 32 (21 to 42) | 38 | 25 (18 to 32) | 0.295 |
| Referral to hospital | 4 | 5 (0 to 10) | 12 | 8 (4 to 12) | 0.414 |
| Paediatric emergency clinic n=167 | n=59 | | n=108 | | |
| Prescription of antibiotics | 11 | 19 (8 to 29) | 19 | 18 (10 to 25) | 0.866 |
| Referral to hospital | 3 | 5 (−1) to 11) | 12 | 11 (5 to 17) | 0.193 |

CRP, C reactive protein; OOH, out-of-hours.

with a total prescription rate of 26% compared with 23% in our study. In two Dutch studies from OOH services, the prescription rate was 36% and 37% for febrile children;[22 23] in a comparable study from paediatric outpatient settings in Sweden and Estonia, the prescription rate was 35% and 61%.[24]

In a comparable study from Norwegian general practice, the total antibiotic prescription rate was 26%, but for otitis media it was only 42% compared with 67% in our study.[25] For pneumonia and tonsillitis, the prescription rates were more similar, 71% and 79%, compared with 67% for both in our study. It seems that the prescription rates in our study were rather low compared with other countries, but correspond well with earlier published Norwegian results. Norway still seems to be a low-prescription country.

The use of CRP at OOH services in Norway is high compared with other countries. In our study, CRP was ordered in 56% of consultations at the OOH services. In a Swedish study, CRP was ordered in 36% of all consultations.[26] Another recently published Swedish study where both children and adults were included found CRP

**Table 3** OR for ordering a CRP test in the group randomised to CRP at request, n=259

| Variable | CRP requested % | OR | CI (95%) | p Value |
|---|---|---|---|---|
| Parents' assessment of sickness | | | | |
| No opinion n=110 | 44 | Ref. | | |
| Viral infection n=69 | 25 | 0.51 | 0.16 to 1.59 | 0.248 |
| Bacterial infection n=79 | 35 | 0.84 | 0.32 to 2.24 | 0.734 |
| Parents' assessment of degree of seriousness | | | | |
| Think it is not serious but want a check n=66 | 17 | Ref. | | |
| Not sure, maybe in need of treatment n=97 | 42 | **4.99** | **1.77 to 14.03** | **0.002** |
| Think antibiotics are needed n=89 | 40 | **5.80** | **1.88 to 17.92** | **0.002** |
| Think the child needs hospitalisation n=6 | 100 | NC | | |
| Respiratory rate* | | 1.01 | 0.97 to1.04 | 0.768 |
| Temperature (°C)* | | **1.64** | **1.08 to2.48** | **0.019** |
| Use of paracetamol during the past 24 h | | | | |
| No n=84 | 24 | Ref. | | |
| Yes n=173 | 42 | 1.43 | 0.59 to 3.42 | 0.428 |
| Fever during the past 24 h | | | | |
| No n=35 | 11 | Ref. | | |
| Yes n=224 | 40 | 2.95 | 0.53 to 16.35 | 0.215 |
| General condition | | | | |
| Normal n=52 | 21 | Ref. | | |
| Ill n=199 | 40 | 1.52 | 0.57 to 3.98 | 0.399 |
| Severely ill n=7 | 71 | 1.30 | 0.14 to 12.02 | 0.817 |
| Type of doctor | | | | |
| Paediatric emergency clinic n=108 | 56 | Ref. | | |
| Out-of-hours services n=151 | 9 | **15.65** | **6.06 to 40.43** | **<0.001** |

Multiple logistic regression analysis.
*Continuous variables.
CRP, C reactive protein; NC, not calculated; Ref., reference.

**Table 4** Distribution of diagnoses, how often CRP is taken on request, CRP values, antibiotic prescription, and referral to hospital for all children

| Diagnosis | Patients, number n=397 | CRP on request, % n=259 | CRP values (mg/L) in pretested group, mean n=138 | CRP values (mg/L) in not pretested group, mean n=259 | Proportion prescribed antibiotic, % n=397 | Proportion referred to hospital, % n=397 |
|---|---|---|---|---|---|---|
| Acute tonsillitis | 47 | 32 | 29 | 45 | 68 | 0 |
| Otitis media | 54 | 40 | 22 | 26 | 67 | 0 |
| Pneumonia | 15 | 80 | 49 | 86 | 67 | 33 |
| URI | 128 | 34 | 15 | 34 | 5 | 2 |
| Viral infection | 31 | 28 | 21 | 16 | 3 | 3 |
| Fever | 20 | 50 | 9 | 54 | 0 | 15 |
| Laryngitis | 17 | 12 | 16 | 19 | 6 | 12 |
| Bronchiolitis | 16 | 10 | 16 | – | 0 | 56 |
| Respiratory infection | 13 | 50 | 27 | 16 | 15 | 0 |
| Cough | 12 | 55 | 7 | 21 | 8 | 8 |
| Asthma | 8 | 17 | 5 | 5 | 12 | 12 |
| Bronchitis | 7 | 50 | 5 | 11 | 42 | 29 |
| Influenza | 5 | 0 | 5 | – | 0 | 20 |
| Gastroenteritis | 5 | 50 | 28 | – | 0 | 40 |
| Pyelonephritis | 2 | 100 | – | 91 | 0 | 100 |
| Other | 17 | 0 | 14 | 11 | 0 | 0 |

CRP, C reactive protein; URI, upper respiratory infection.

testing in 38% and that CRP pretesting correlated with increased antibiotic prescription.[27]

The effect of CRP testing on antibiotic prescription has been studied in several settings, with conflicting results. For adult patients, no effect was found for acute bronchitis[28] or acute pharyngitis.[14] However, in other studies of respiratory tract infections, CRP testing has resulted in lower prescription rates.[15 16 29] For children, there are fewer studies, but one systematic review from 2011 analysed which CRP values that could be diagnostically useful when trying to rule in or rule out serious infections.[10] Another study that included clinical signs and CRP in a prediction model found it useful for estimating pneumonia and other serious bacterial infections.[30] Common for most other studies that look at the effect CRP testing has on antibiotic prescription, is that CRP is used as an intervention in settings where CRP rarely is used. In contrast, we have studied what happens in a low-prevalent population, where CRP is easily accessible, where normal practice and economic incentives stimulate to use CRP very often.

### Implications for research and practice

Antibiotic prescription rates in Norway are relatively low compared with other countries, but still higher than recommended, and many prescriptions do not follow the national guidelines for antibiotic prescription.[7] The extensive use of CRP in Norway and a tendency towards screening every febrile child with a CRP test, often before the consultation, is not according to any recommendations. There is no evidence for benefit of this practice. Our study shows that CRP screening does not reduce antibiotic prescription rates; the trend is rather an increase. Possibly, prescription rates are increased due to more often false positive CRP values when the test is taken so often at children with low risk of serious infections. Training in communication skills may affect prescription rates,[29] and should be given priority over extensive laboratory testing in this setting.

Widespread use of antibiotics for otitis media and tonsillitis, such as found in our study, is not recommended according to the national guidelines. The same goes for antibiotic prescriptions for unspecific diagnoses such as cough and upper respiratory infections.

Further studies should focus on how to reduce clinicians' uncertainty with the use of clinical prediction rules validated for low-prevalent populations, and training in communication skills to reduce parents' concern.

## CONCLUSION

CRP is extensively used in children at Norwegian OOH services, especially when the child has high fever, or if the parents think it is a serious infection. CRP screening of all children with fever and/or respiratory infections will not reduce the prescription of antibiotics.

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# Out-of-hours antibiotic prescription after screening with C reactive protein: a randomised controlled study

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IV

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# 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

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## ABSTRACT

**Objectives:** Acute respiratory infections and fever among children are highly prevalent in primary care. It is challenging to distinguish between viral and bacterial infections. Norway has a relatively low prescription rate of antibiotics, but it is still regarded as too high as the antimicrobial resistance is increasing. The aim of the study was to identify predictors for prescribing antibiotics or referral to hospital among children.

**Design:** Secondary analysis of a randomised controlled study.

**Setting:** 4 out-of-hours services and 1 paediatric emergency clinic in Norwegian primary care.

**Participants:** 401 children aged 0–6 years with respiratory symptoms and/or fever visiting the out-of-hours services.

**Outcomes:** 2 main outcome variables were registered: antibiotic prescription and referral to hospital.

**Results:** The total prescription rate of antibiotics was 23%, phenoxymethylpenicillin was used in 67% of the cases. Findings on ear examination (OR 4.62; 95% CI 2.35 to 9.10), parents' assessment that the child has a bacterial infection (OR 2.45; 95% CI 1.17 to 5.13) and a C reactive protein (CRP) value >20 mg/L (OR 3.57; 95% CI 1.43 to 8.83) were significantly associated with prescription of antibiotics. Vomiting in the past 24 hours was negatively associated with prescription (OR 0.26; 95% CI 0.13 to 0.53). The main predictors significantly associated with referral to hospital were respiratory rate (OR 1.07; 95% CI 1.03 to 1.12), oxygen saturation <95% (OR 3.39; 95% CI 1.02 to 11.23), signs on auscultation (OR 5.57; 95% CI 1.96 to 15.84) and the parents' assessment before the consultation that the child needs hospitalisation (OR 414; 95% CI 26 to 6624).

**Conclusions:** CRP values >20 mg/L, findings on ear examination, use of paracetamol and no vomiting in the past 24 hours were significantly associated with antibiotic prescription. Affected respiration was a predictor for referral to hospital. The parents' assessment was also significantly associated with the outcomes.

**Trial registration number:** NCT02496559; Results.

## Strengths and limitations of this study

- Nearly complete data since we used dedicated nurses to collect clinical symptoms and findings on all children.
- Multiple explanatory variables collected on nearly all children.
- Wide inclusion criteria showing the variety of diagnoses and conditions treated at OOH services.
- Validity of diagnoses is weak in primary care and often not possible to verify.
- This study is based on a randomised study where every third child got a C reactive protein (CRP) test. This may have resulted in more elevated CRP values than would otherwise have been found.

## INTRODUCTION

Acute childhood infections are highly prevalent in primary care. Most infections are self-limiting and the prevalence of serious bacterial infections is decreasing,[1] but still challenging to distinguish from self-limiting illness. One important reason for the decline in serious infections in Norway is vaccines. Haemophilus influenza type B (HIB) was the most frequent cause of meningitis, epiglottis and other invasive infections in young children in Norway before the vaccine was introduced in the childhood immunisation schedule in 1992. After the vaccine was introduced, these infections practically disappeared. The annual incidence of invasive pneumococcal infections fell from

75 to around 10 cases per 100 000 after the introduction of pneumococcal conjugate vaccines in 2006.[2]

There exists no decision score system for children for use in primary care. Pediatric Early Warning Score has been evaluated in hospitals, and this tool has been found valuable in quantifying patient status, early recognition of clinical deterioration and promoting communication.[3] It has not been investigated for use in primary care where the prevalence of serious infections is lower. Other studies have shown the utility of a scoring system to stratify children with acute infections, but still there is a need of validation for use in primary care.[4–6]

Near patient testing in primary care has expanded in Norway as in other Scandinavian countries.[7] The most used test is C reactive protein (CRP), an inflammation marker reflecting the severity of inflammation and tissue injury and used by many as a tool to differentiate between bacterial and viral infections. It has been popular in Norwegian primary care as a point-of-care test, used in more than 50% of all consultations with children with respiratory symptoms and infections.[8] To order the test seems more like a routine than a supplement to history taking and clinical examination. It is possible that the test is used to assure parents that there is no serious bacterial infection. It is also possible that the widespread use may have economic reasons.[9] The test result is difficult to interpret, especially for low values between 20 and 50 mg/L.[10 11] Urine dipstick, haemoglobin and Strep A test are also available at most services. Strep-A test is recommended for differentiation between bacterial and viral throat infections.[12] Measurement of oxygen saturation with pulse oximeters has been more available for children in emergency departments. Earlier studies have seen a connection with increased use and increased hospitalisation.[13] How it affects the referral rate from primary care is not known.

Since 2010, the prescription rate of antibiotics has been relatively stable in Norway but decreased slightly in 2013–2014.[14] In Scandinavia, Sweden has a lower prescription rate (13.0 DDD per 1000 inhabitants per day), while Denmark has the same rate as Norway (15.9 DDD per 1000 inhabitants per day).[15] Still, the prescription rate is regarded as too high and it is a national strategy to try to reduce it by 20–30%.[16] National guidelines for the use of antibiotics in primary care have been published from the Norwegian Directorate of Health.[17] The guidelines are well known among primary care physicians, but it is not known to what extent they are followed.

Before admission to hospital in Norway, a patient must be evaluated by a general practitioner (GP) or at an out-of-hours service. In total 80% of all antibiotics are prescribed in primary care. To reduce the prescription rate and to properly select children in need of treatment at hospitals, we need to know more about what is predicting the two actions.

The aim of the present study was therefore to identify predictors for antibiotic prescription and referral to hospital in a primary care setting.

## METHOD

We included children aged 0–6 years with fever and/or respiratory symptoms. The data consist of (1) clinical symptoms and signs collected by a nurse at the OOH services before the doctor's consultation, (2) the medical record and (3) a questionnaire filled in by the parents before the consultation. Every third child was randomised to a CRP test before the consultation. The remaining 2/3 received usual care, allowing the doctor to order a CRP test on individual indication. The results of the randomised trial have been reported elsewhere.[18]

### Inclusion and procedures

The inclusion of participants took place during the winter seasons from January 2013 until May 2015 at four different OOH services near Bergen and at one paediatric emergency clinic at Haukeland University Hospital in Bergen. This emergency clinic is a walk-in, open-access facility, and is located at a hospital and staffed by paediatricians.

The nurses at the OOH services were informed about the study inclusion criteria and examination procedures. At the paediatric emergency clinic, two trained nurses were engaged especially for the project. The parents were approached by the nurse and invited to participate in the study and fill out a questionnaire prior to the consultation. The nurse did a clinical examination on all children and a CRP test on every third child. The CRP result followed the patient to the consultation. The diagnosis and treatment were recorded from the medical record after the consultation.

### Variables

The two main outcome variables were antibiotic prescription and referral to hospital. Recorded variables from the medical history were age, gender, previous chronic disease, duration of present illness, fever in the past 24 hours, variation in fever, vomiting, earache, coughing, dyspnoea, throat symptoms, diarrhoea, reduced diuresis, cervical rigidity, skin rash, and use of paracetamol or ibuprofen in the past 24 hours. The parents' assessment of the illness and its seriousness was also recorded. Variables from the nurse's examination were temperature, respiratory rate, oxygen saturation, the degree of hydration, capillary refill time and general condition on a three-point scale (normal, ill and severely ill). From the medical record, we noted signs on auscultation and at ear examination, if not mentioned in the record, it was coded as missing. Finally, we recorded whether the doctor was a paediatrician or working at the OOH services.

### Statistical analysis

Means were analysed with Student's t-tests and proportions with $\chi^2$ tests. Logistic regression analyses were performed to analyse predictors for the two main outcomes: prescription of antibiotics and referral to hospital. Explanatory variables significant ($p<0.05$) in bivariate analyses were included in the final regression model. All variables with missing values were imputed in the final model. Multiple imputations with a fully conditional specification method producing five imputed data sets were performed and the results pooled. Hosmer-Lemeshow tests were used to test the goodness-of-fit. Significance level was set at 5% ($p<0.05$). Data were analysed using IBM SPSS Statistics V.23.

## RESULTS

A total of 401 children were recruited for the study, but 4 left the clinic before the doctor's consultation, leaving 397 for inclusion in our analyses. The mean age was 2.3 years (median 1.6), and 55.6% were boys.

### Prescription of antibiotics

A total of 93 patients (23%) got a prescription of antibiotics. Phenoxymethylpenicillin (PcV) was used most often, and amoxicillin to a lesser extent (table 1). The distribution of diagnoses and prescriptions at different CRP levels is shown in table 2. In the group with CRP 21–40 mg/L, more than 40% got a prescription, compared with nearly all in the group with CRP>80 mg/L (figure 1).

For pneumonia, all got antibiotics if not referred to hospital. For the other diagnoses, there was a clear tendency that higher CRP led to a higher prescription rate. There was a discrepancy between earache and findings with otoscopy; 129 had signs of ear infection with otoscopy and 103 had earache, but only 63 had both. In total, 42% of all with signs of infection or earache got a diagnosis of otitis media and an antibiotic prescription.

If the parents thought it was a bacterial infection and that antibiotics were needed 39% got a prescription (table 3).

**Table 1** Distribution of different types of antibiotics prescribed

| Antibiotics | Number | Per cent |
|---|---|---|
| Phenoxymethylpenicillin | 62 | 66.7 |
| Amoxicillin | 19 | 20.4 |
| Erythromycin (macrolide) | 8 | 8.6 |
| Clindamycin | 3 | 3.2 |
| Unknown | 1 | 1.1 |
| Total | 93 | 100 |

### Referrals

A total of 31 patients (8%) were referred to hospital. The most common diagnoses among the referred patients were asthma, bronchiolitis and pneumonia. Two had gastroenteritis and two had pyelonephritis (table 2). If the parents assessed the child to need hospitalisation 86% were referred to hospital (table 3).

### Predictor analyses

Explanatory variables significant in bivariate analyses are shown in table 4. Ear examination was missing in 17% of cases, oxygen saturation in 14% of all cases, and the remainder in <10%. Imputed variables were: vomiting, respiratory rate, oxygen saturation, findings on auscultation and ear examination, parents' assessment, earache, use of paracetamol and temperature measurement.

#### Prescription of antibiotics

Findings on ear examination, use of paracetamol and no vomiting in the past 24 hours all remained significantly associated with prescription of antibiotics in the multiple regression analysis after multiple imputations (table 5). CRP>20 mg/L was significantly associated with prescription. The parents' assessment that their child had a bacterial infection was also associated with increased prescription rate. The Hosmer-Lemeshow test for this analysis showed good fitness of the model with p=0.540 before imputation and p=0.805 after imputation.

#### Referrals

The strongest predictor for referral to hospital was affected respiration. No findings on ear examination, a high respiratory rate, obstructive signs on auscultation and reduced oxygen saturation were significantly associated

**Table 2** Distribution of diagnoses and number of AB prescriptions in different CRP value (mg/L) groups (%) (n=397)

| Diagnoses | Referral to hospital | AB | AB when CRP not taken | AB when CRP<21 | AB when CRP 21–40 | AB when CRP 41–60 | AB when CRP>60 |
|---|---|---|---|---|---|---|---|
| Acute tonsillitis (47) | 0 | 32 | 11 (69) | 5 (38) | 8 (89) | 3 (75) | 5 (100) |
| Otitis media (54) | 0 | 36 | 14 (58) | 10 (63) | 7 (78) | 3 (100) | 2 (100) |
| Pneumonia (15) | 5 | 10 | 1 (100) | 3 (100) | 1 (100) | 2 (100) | 3 (100) |
| URI (194) | 6 | 10 | 1 (1) | 1 (1) | 1 (5) | 4 (44) | 3 (60) |
| Fever/cough/other (49) | 5 | 1 | 0 | 0 | – | 1 (100) | – |
| Asthma/bronchiolitis (31) | 11 | 4 | 2 (15) | 0 | 2 (100) | – | 0 |
| GE/dehydration (5) | 2 | 0 | – | – | – | – | – |
| Pyelonephritis (2) | 2 | 0 | – | – | – | – | – |
| Total number in the group | 31 | 93 | 153 (19) | 132 (14) | 45 (42) | 20 (65) | 16 (81) |

AB, antibiotics; CRP, C reactive protein; GE, gastroenteritis; URI, upper respiratory infections.

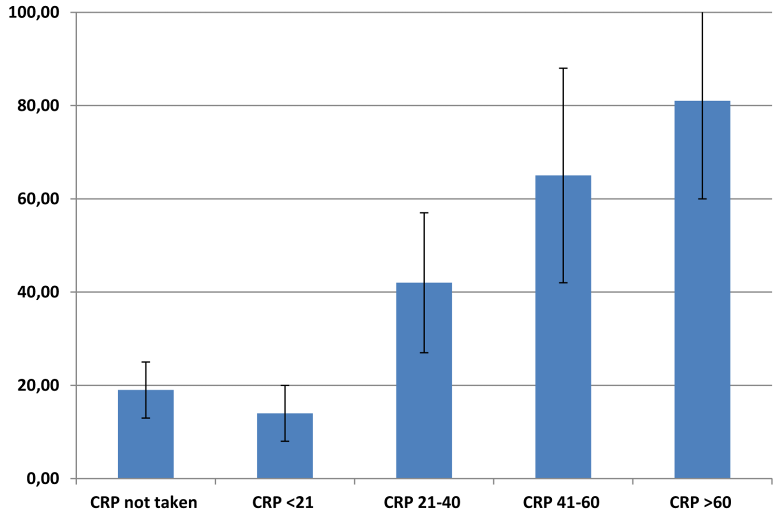


**Figure 1** Antibiotic prescription rates (%) with 95% CI at different C reactive protein (CRP) levels (n=366).

**Table 3** Parents' assessment and prescription of antibiotics and referral to hospital

| Variable | Prescription of antibiotics, number (%) | Referral to hospital, number (%) |
|---|---|---|
| Parents' assessment of sickness | | |
| No opinion, n=177 | 34 (19) | 12 (7) |
| Viral infection, n=101 | 14 (14) | 12 (12) |
| Bacterial infection, n=116 | 45 (39) | 7 (6) |
| Parents' assessment of degree of seriousness | | |
| Think it is not serious but want a check, n=103 | 12 (12) | 3 (3) |
| Not sure, maybe in need of treatment, n=149 | 37 (25) | 15 (10) |
| Think antibiotics are needed, n=134 | 44 (33) | 6 (5) |
| Think the child needs hospitalisation, n=7 | 0 | 6 (86) |

with referral to hospital, as well as the parents' assessment of disease severity (table 6). All remained significant after imputation. The Hosmer-Lemeshow test was significant before imputation (p=0.006) but not after (0.105), showing that the model with imputation gave the best fit.

## DISCUSSION

### Summary

According to Norwegian guidelines, the preferred antibiotic for respiratory tract infections is PcV. This study showed this drug to be used for 2/3 of all children treated with antibiotics. CRP values >20 mg/L, use of paracetamol in the past 24 hours and signs on ear examination were the main predictors of antibiotic prescription. Increased respiratory rate and signs on auscultation were significantly associated with hospital referrals. Parents' assessments of sickness and seriousness were also significantly associated with outcomes. The prescription rate increased already with CRP values >20 mg/L, not according to the national guidelines which recommend clinical observations when CRP values are <50–100 mg/L.

### Strengths and limitations

Our data are nearly complete due to the effort of the nurses. Collecting data from the medical record alone would have been simpler and may have increased the number of included children, but would have caused more missing data.

The children who were seen by a paediatrician at the paediatric emergency clinic were unselected and not referred from primary care. At the OOH services, the doctor is a GP, a GP in training or other specialists or locums. We have no detailed information about the experience of these OOH doctors, but know that younger doctors are working more often at OOH-services and make more use of CRP.[9] How the experience affects prescription is not known, but in our study we did not find a significant association between being a paediatrician and prescription.

Validity of diagnoses is weak in primary care and often not possible to verify. Many use symptom diagnoses as fever and cough. Most infections in primary care are viral infections and self-limiting infections such as otitis media and acute tonsillitis. The given diagnosis may

Table 4 Prescription of antibiotics and referral to hospital in different groups (bivariate analyses)

| | | Prescription of antibiotics | | | Referral to hospital | | |
|---|---|---|---|---|---|---|---|
| Variables | N | Yes | No | p Value | Yes | No | p Value |
| Means | | | | | | | |
| Age | 397 | 2.61 | 2.25 | 0.098 | 1.69 | 2.39 | 0.040 |
| Temperature measured | 385 | 38.22 | 37.92 | 0.013 | 38.19 | 37.98 | 0.245 |
| Respiratory rate | 365 | 31.11 | 33.08 | 0.246 | 48.28 | 31.30 | <0.001 |
| Proportions | | | | | | | |
| *CRP value (mg/L)* | 397 | | | | | | |
| Not taken | 164 | 0.18 | 0.82 | | 0.07 | 0.93 | |
| CRP<21 | 142 | 0.13 | 0.87 | | 0.07 | 0.93 | |
| CRP 21–40 | 48 | 0.40 | 0.60 | | 0.06 | 0.94 | |
| CRP 41–60 | 22 | 0.59 | 0.41 | | 0.09 | 0.91 | |
| CRP>60 | 21 | 0.62 | 0.38 | <0.001 | 0.24 | 0.76 | 0.089 |
| *Oxygen saturation* | 340 | | | | | | |
| >95% | 227 | 0.22 | 0.78 | | 0.05 | 0.95 | |
| 90–95% | 104 | 0.21 | 0.79 | | 0.13 | 0.87 | |
| <90% | 9 | 0.22 | 0.78 | 0.984 | 0.33 | 0.67 | 0.001 |
| *Parents' assessment of seriousness* | 393 | | | | | | |
| Think it is not serious but want a check | 103 | 0.12 | 0.88 | | 0.03 | 0.97 | |
| Not sure, maybe in need of treatment | 149 | 0.25 | 0.75 | | 0.10 | 0.90 | |
| Think antibiotics are needed | 134 | 0.33 | 0.67 | | 0.05 | 0.95 | |
| Think the child needs hospitalisation | 7 | 0 | 0.02 | 0.001 | 0.86 | 0.14 | <0.001 |
| *Parents' assessment of sickness* | 394 | | | | | | |
| No opinion | 177 | 0.19 | 0.81 | | 0.07 | 0.93 | |
| Viral infection | 101 | 0.14 | 0.86 | | 0.12 | 0.88 | |
| Bacterial infection | 116 | 0.39 | 0.61 | <0.001 | 0.06 | 0.94 | 0.215 |
| Paediatrician | 167 | 0.18 | 0.82 | | 0.09 | 0.91 | |
| Doctors working at OOH services | 230 | 0.27 | 0.73 | 0.029 | 0.07 | 0.93 | 0.458 |
| Vomiting on last day | 242 | 0.16 | 0.84 | | 0.12 | 0.88 | |
| Not vomiting on last day | 153 | 0.29 | 0.71 | 0.003 | 0.05 | 0.95 | 0.021 |
| Earache in the past 24 hours | 103 | 0.42 | 0.58 | | 0.05 | 0.95 | |
| No earache in the past 24 hours | 290 | 0.17 | 0.83 | <0.001 | 0.09 | 0.91 | 0.184 |
| Dyspnoea in the past 24 hours | 225 | 0.25 | 0.75 | | 0.11 | 0.89 | |
| No dyspnoea in the past 24 hours | 171 | 0.21 | 0.79 | 0.522 | 0.04 | 0.96 | 0.052 |
| Paracetamol in the past 24 hours | 264 | 0.30 | 0.70 | | 0.08 | 0.92 | |
| No use of paracetamol in the past 24 hours | 131 | 0.10 | 0.90 | <0.001 | 0.08 | 0.92 | 0.775 |
| Findings on ear examination | 129 | 0.58 | 0.42 | | 0.02 | 0.98 | |
| No findings on ear examination | 200 | 0.14 | 0.86 | <0.001 | 0.10 | 0.90 | 0.011 |
| Signs on auscultation | 83 | 0.22 | 0.78 | | 0.24 | 0.76 | |
| No signs on auscultation | 281 | 0.21 | 0.79 | 0.837 | 0.04 | 0.96 | <0.001 |
| Randomised to CRP pretest test | 138 | 0.26 | 0.74 | | 0.05 | 0.95 | |
| Randomised to usual care | 259 | 0.22 | 0.78 | 0.362 | 0.09 | 0.91 | 0.139 |

CRP, C reactive protein.

often just reflect the treatment. If otitis is found in addition to upper respiratory infection, the main diagnosis may be otitis media if antibiotics are prescribed and upper respiratory infection if antibiotics are not prescribed. It is not possible from this material to estimate the prescription rate for acute otitis media or tonsillitis.

This observational study is based on a randomised study where every third child got a CRP test before the consultation. This may have increased the total number of CRP tests, and may have resulted in more elevated CRP than would otherwise have been found. It is possible that this may have affected the prescription rate.

The doctors were informed about the study, a fact which may also have affected the outcomes.

## Comparison and implications

We found in our study a total prescription rate of 23%, but a higher prescription of amoxicillin (20%) than expected from guidelines.[17] This is probably due to the bad taste of PcV mixtures; many will prefer the amoxicillin variants if they have tried it before.[19] A recent Norwegian study found a total prescription rate of 26% and nearly the same amount of amoxicillin (26%).[20] We found a higher prescription of PcV (67% compared with 42%) and a lower use of macrolides (9% compared with 30%). This reduction in the use of macrolides has been

**Table 5** OR for prescribing antibiotics by different variables and parents' assessment. Significant results (p<0.05) in bold

| Variable | Complete case, n=294 (missing 26%) OR | 95% CI | Multiple imputation OR | 95% CI |
|---|---|---|---|---|
| Temperature measured* | 1.14 | 0.78 to 1.66 | 1.11 | 0.78 to 1.57 |
| Paediatrician (no=0, yes=1) | 0.73 | 0.33 to 1.61 | 0.83 | 0.43 to 1.62 |
| Vomiting on last day (no=0, yes=1) | **0.26** | **0.11 to 0.60** | **0.26** | **0.13 to 0.53** |
| Earache in the past 24 hours (no=0, yes=1) | 1.41 | 0.66 to 3.03 | 1.71 | 0.89 to 3.28 |
| Findings on ear examination (no=0, yes=1) | **4.22** | **1.98 to 9.00** | **4.62** | **2.35 to 9.10** |
| Signs on auscultation (no=0, yes=1) | 1.62 | 0.64 to 4.10 | 1.57 | 0.68 to 3.63 |
| Paracetamol in the past 24 hours | 2.13 | 0.88 to 5.13 | **2.35** | **1.11 to 4.96** |
| CRP value (mg/L) | | | | |
| Not taken (reference) | | | | |
| CRP<21 | 0.66 | 0.27 to 1.63 | 0.71 | 0.33 to 1.55 |
| CRP 21–40 | **3.39** | **1.22 to 9.43** | **3.57** | **1.43 to 8.83** |
| CRP 41–60 | **13.32** | **3.39 to 52.37** | **10.11** | **3.07 to 33.34** |
| CRP>60 | **11.33** | **2.84 to 45.12** | **10.19** | **2.84 to 36.49** |
| Parents' assessment of seriousness | | | | |
| Think it is not serious but want a check (reference) | | | | |
| Not sure, maybe in need of treatment | 1.38 | 0.49 to 3.89 | 1.27 | 0.52 to 3.12 |
| Think antibiotics are needed | 1.63 | 0.56 to 4.75 | 1.41 | 0.55 to 3.62 |
| Think the child needs hospitalisation | 0.00 | 0.00 to 0.00 | 0.00 | 0.00 to 0.00 |
| Parents' assessment of sickness | | | | |
| No opinion (reference) | | | | |
| Viral infection | 0.73 | 0.28 to 1.93 | 0.89 | 0.38 to 2.10 |
| Bacterial infection | 1.78 | 0.79 to 4.01 | **2.45** | **1.17 to 5.13** |

Adjusted logistic regression with and without multiple imputation.
*Continuous variable.
CRP, C reactive protein.

**Table 6** OR for referral to hospital by different variables and parents' assessment. Significant results (p<0.05) in bold

| Variable | Complete cases n=245 (missing 38%) OR | 95% CI | Multiple imputation OR | 95% CI |
|---|---|---|---|---|
| Age* | 1.30 | 0.87 to 1.94 | 1.02 | 0.71 to 1.46 |
| Vomiting (no=0, yes=1) | 0.85 | 0.23 to 3.18 | 1.09 | 0.40 to 2.97 |
| Respiratory rate* | **1.05** | **1.00 to 1.11** | **1.07** | **1.03 to 1.12** |
| Oxygen saturation | | | | |
| >95% (reference) | | | | |
| 90–95% | **4.28** | **1.05 to 17.43** | **3.39** | **1.02 to 11.23** |
| <90% | 16.03 | 0.96 to 267.81 | 3.19 | 0.32 to 31.94 |
| Signs on auscultation (no=0, yes=1) | **6.92** | **1.73 to 27.64** | **5.57** | **1.96 to 15.84** |
| Findings on ear examination (no=0, yes=1) | **0.19** | **0.04 to 0.98** | **0.22** | **0.05 to 0.87** |
| Parents' assessment of seriousness | | | | |
| Think it is not serious but want a check (reference) | | | | |
| Not sure, maybe in need of treatment | **14.61** | **1.13 to 188.48** | **6.37** | **1.34 to 30.18** |
| Think antibiotics are needed | 7.08 | 0.52 to 96.80 | 3.80 | 0.73 to 19.84 |
| Think the child needs hospitalisation | **815.72** | **26.58 to 25033.0** | **414.17** | **25.89 to 6624.4** |

Adjusted logistic regression with and without multiple imputation.
*Continuous variable.

observed in primary care in Norway in the past decade.[15] Hopefully, this trend reflects the efforts to decrease the prescription rates of antibiotics and to avoid broad-spectrum antibiotics.

The diagnoses are not comparable from study to study. We found a high prescription rate for otitis media (67%). However, only 42% of those with signs of otitis media got a prescription of antibiotics. This is the same rate as in the mentioned Norwegian study,[20] implying that the diagnoses reflect the treatment given. For the diagnoses usually considered to be of bacterial origin as pneumonia, otitis media and tonsillitis, the prescription rate was high even in the presence of low CRP values, but was increasing with increasing CRP values. For diagnoses of unspecific or typical viral origin, there was no prescription with negative CRP (≤20 mg/L) and rising prescription rate at higher CRP values. These results are comparable to data from a Swedish study from 1999 to 2005, but generally prescription rates were higher in this period.[21] A more recent study from the UK also showed the same tendency: a strong association between the diagnoses and prescription rates and weaker association between abnormal examination findings and prescription.[22]

The strongest predictor for prescription in our study was a CRP value >20 mg/L. A value ≤20 mg/L has been found to be useful as a cut-off value for ruling out serious infections.[11] Nevertheless, in our study, 13% of those with a CRP value <20 mg/L got a prescription for antibiotics. This may reflect a general lack of confidence in the CRP test, but it is also possible that the clinical condition of the patients in these cases implied a bacterial aetiology, leading the doctor to judge the test result as false negative. The guidelines recommend expectance when CRP is below 50–100 mg/L at day 2 and later.[17] Our study shows that the guidelines are often not followed. There may be a potential for further reducing the prescription rate, by using the recommended CRP limits.

The parents' assessments were collected by a questionnaire prior to the consultation. They were just given three choices: no opinion, viral infection and bacterial infection, and were also asked if they thought their child was in need of treatment. There was a strong association between the parents' opinion and the given treatment. This may reflect that the parents know and assess their child well. This may be an important explanation, especially for admission to hospital. However, for prescription, this may also reflect earlier studies that clinicians often prescribe because parents want a prescription.[23] Earache was also significantly associated with increased prescription rate. A Dutch study from 2012 found that concerned parents, ill appearance, signs of throat infection and earache were significantly associated with prescription of antibiotics.[24] They also found that only a small proportion of the prescriptions were explained by signs and symptoms, and that other non-medical-based considerations may have played a role in the decisions.

Outside Europe, in developing countries the situation is very different in terms of the prescribing rate and what is prescribed. Comparison is difficult due to little regulation of prescribing and self-medication, and there are few publications from primary care.[25] From China and India, there are published studies showing prescribing rates of 50–74% in rural areas and a high usage of broad-spectrum antibiotics.[26–28] A qualitative study found that poor knowledge of village doctors, patients' demands and financial incentives were important factors affecting the prescription.[29] The spread of antimicrobial resistance has led to increased mortality and is especially harmful for small children in areas with a lower standard of sanitation and public health, and a higher prevalence of serious infectious diseases.[30] Education, better communication between physicians and parents, diagnostic tests and regulation of the prescription are important factors to influence the development in the right direction. Lessons learnt from efforts to reduce prescription in developed countries may also be used for this purpose.

For the second outcome, referral to hospital, the predictors were different. The main reasons for referral were affected respiration, reflecting the diagnoses most often referred: asthma/bronchiolitis and pneumonia. The respiratory rate and oxygen saturation were measured by the nurses and coincided well with the doctors' opinion of how ill the child was, as well as the parents' assessment of the seriousness. The nurses are the first persons meeting the children at the OOH service and it seems that examination of the child's respiration should be prioritised first, especially when the waiting time to see the doctor is long. All nurses and other staff in the reception of the OOH services should be educated in examination of the child's respiration to be better able to prioritise correctly.

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