Linköping University Medical Dissertation No. 1746

Diagnosing pneumonia in primary care

Aspects of the value of clinical and laboratory
findings and the use of chest X-ray

Anna Moberg

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findings and the use of chest X-ray

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*To Jonas,
Elsa and Alice*

“Sometimes it’s okay if the only thing you did today was breathe”
Yumi Sakugawa

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ABSTRACT

It is important to identify patients with pneumonia because it is potentially a serious disease, often of bacterial origin, that should be treated with antibiotics. It is equally important to identify those with acute bronchitis, a self-limiting disease, that should not be treated with antibiotics. Because bacterial resistance is increasing, overprescribing of antibiotics should be avoided. However, it is sometimes difficult to differentiate between the two diagnoses, and guidelines concerning the assessment do not conform.

The general aim of this thesis was to investigate if diagnostics of pneumonia in primary care can be improved and whether this could contribute to reduced prescription of antibiotics.

As a first step, different anamnestic, clinical and laboratory findings and the doctor's degree of suspicion of pneumonia in primary care were compared with chest X-ray (CXR) findings. The doctor's degree of suspicion of pneumonia was shown to be a good predictor. When the physician was sure of the diagnosis, the likelihood for radiographic pneumonia was high and when quite sure, CXR was positive in less than half of the cases.

To further improve the diagnostics of pneumonia, and thus reduce antibiotic prescriptions, patients were referred for CXR when the physician was unsure or quite sure of a pneumonia diagnosis. The intervention did not result in any decrease in antibiotic prescriptions compared with a control group. However, it emerged that the physicians did not fully trust the CXR outcome, but prescribed antibiotics even when the results were negative.

To gain insight into the contribution of C-reactive protein (CRP) levels to the degree of suspicion, physicians were asked to estimate their degree of suspicion of pneumonia before and after CRP testing. CRP affected the degree of suspicion to a great extent, and most often resulted in a lowered degree of suspicion and thereby in the clinical decision of dismissing the diagnosis of pneumonia.

The use of different diagnostic tests and prescription of antibiotics in the assessment of acute bronchitis and pneumonia over time was evaluated in a register-based study. The study showed that the use of diagnostic tests for both diagnoses has increased, and that there has been a reduction in antibiotic prescriptions for acute bronchitis.

In conclusion, the doctor's degree of suspicion of pneumonia seems to be a good predictor of the condition. When the physician is sure of the diagnosis, no further investigation is needed, and antibiotics can be

prescribed on reliable grounds. CRP testing affects the degree of suspicion and is most valuable when unsure of the diagnosis where it can be helpful to exclude pneumonia. In contrast, more extensive use of CXR does not contribute to a decrease in antibiotic prescriptions in the diagnostics of pneumonia.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Lunginflammation (pneumoni) och luftrörskatarr (akut bronkit) räknas till nedre luftvägsinfektioner. Eftersom lunginflammation är en allvarlig sjukdom, som ofta är orsakad av bakterier, bör den behandlas med antibiotika. Luftrörskatarr är däremot en självläkande sjukdom som oftast orsakas av virus och antibiotikaförskrivning bör därför undvikas. Då antibiotikaresistensen ökar bör överförskrivning av antibiotika undvikas. Därför är det viktigt att läkaren ställer rätt diagnos. Ibland är det dock svårt att skilja diagnoserna åt och riktlinjerna för diagnostik skiljer sig mellan länder.

Det övergripande syftet med min avhandling var att undersöka om diagnostiken av lunginflammation i primärvården kan förbättras och om det skulle kunna bidra till minskad förskrivning av antibiotika. I den första studien jämfördes olika undersökningsfynd och läkarens grad av misstanke om lunginflammation med lungröntgenresultat. Läkarens misstanke om lunginflammation visade sig vara en bra prediktor när misstankegraden värderades som 'säker'. När misstankegraden värderades som 'ganska säker' var lungröntgen positiv i mindre än hälften av fallen.

För att ytterligare skärpa diagnostiken och minska antibiotikaförskrivningen gjordes en uppföljande interventionsstudie. Patienter remitterades för lungröntgenundersökning när läkaren misstänkte lunginflammation men inte var helt säker på diagnosen. Resultaten jämfördes med en kontrollgrupp. Interventionen resulterade inte i någon minskad förskrivning av antibiotika. Det visades sig däremot att läkarna inte helt litade på lungröntgenresultatet utan till viss del föreskriver antibiotika även när röntgen är normal.

I vilken utsträckning analys av C-reaktivt protein (CRP) bidrar till läkarens misstanke om lunginflammation undersöktes genom att läkare fick värdera sin misstankegrad före och efter testning. CRP-resultatet visade sig påverka graden av misstanke i stor utsträckning, och ofta leda till att misstanken om lunginflammation kunde avfärdas.

Användningen av diagnostiska tester och antibiotikaförskrivning över tid vid nedre luftvägsinfektioner undersöktes i en registerstudie.

Antibiotikaförskrivningen har visat sig minska vid luftrörskatarr samtidigt som användning av diagnostiska tester ökat vid diagnostik av både luftrörskatarr och lunginflammation.

Sammanfattningsvis är läkarens misstanke om lunginflammation en bra prediktor för lunginflammation och när läkaren är säker på diagnosen behövs ingen vidare utredning utan antibiotika kan förskrivas på trovärdiga grunder. CRP påverkar läkarens misstanke om lunginflammation i hög grad och när läkaren är osäker på diagnosen kan CRP bidra till att misstanke kan avfärdas. Ökad användning av diagnostiska tester vid diagnostik av luftrörskatarr och lunginflammation indikerar ett behov av diagnostiska hjälpmedel. Resultaten stödjer våra svenska riktlinjer där CRP och lungröntgen inte rekommenderas i den initiala handläggningen men kan övervägas vid oklar nedre luftvägsinfektion.

LIST OF PAPERS

- I. **Moberg AB**, Taléus U, Garvin P, Fransson S-G, Falk M: Community-acquired pneumonia in primary care: clinical assessment and the usability of chest radiography. *Scandinavian Journal of Primary Health Care*. 2016;34(1):21-27.
- II. **Moberg AB**, Kling M, Paues J, Fransson SG, Falk M: Use of chest X-ray in the assessment of community-acquired pneumonia in primary care – an intervention study. *Scandinavian Journal of Primary Health Care*. 2020;38:323-329.
- III. **Moberg AB**, Ravell-Jensen A, Paues J, Falk M: C-reactive protein influences the doctor's degree of suspicion of pneumonia in primary care – a prospective observational study. *Submitted*.
- IV. **Moberg AB**, Cronberg O, Falk M, Hedin K. Change in the use of diagnostic tests in the management of lower respiratory tract infections: a register-based study in primary care. *BJGP Open*. 2020;4:bjgpopen20X101015.

ABBREVIATIONS

AUC	Area under curve
CAP	Community-acquired pneumonia
CDR	Clinical decision rule
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRP	C-reactive protein
CXR	Chest X-ray
EHR	Electronic health record
GP	General practitioner
HRCT	High-resolution computed tomography
IPD	Invasive pneumococcal disease
LRTI	Lower respiratory tract infection
LU	Lung ultrasonography
MIC	Minimal inhibitory concentration
NPV	Negative predictive value
PBP	Penicillin-binding protein
PCT	Procalcitonin
PHCC	Primary health care centre
POCT	Point-of-care test
PPV	Positive predictive value
URTI	Upper respiratory tract infection
WBC	White blood cell

OVERVIEW OF THE THESIS

Table 1

	Paper I	Paper II	Paper III	Paper IV
Aim	To investigate the diagnostic value of clinical and laboratory findings in patients with pneumonia, and to explore the association between the physician's degree of suspicion and CXR results, and to evaluate if CXR should be used routinely in primary care	To explore the benefit of using CXR when the physician is not sure of the diagnosis of pneumonia, and if using CXR this way results in lowered antibiotic prescription rate	To investigate to what extent the physician's degree of suspicion of pneumonia is affected by the CRP level in primary care	To calculate the proportion of diagnostic tests in the management of LRTIs in Swedish primary care, and to evaluate if the use has changed over time. The secondary aim was to investigate if the prescription pattern changed over time
Methods	Prospective observational study of patients aged 18 years, presenting with LRTIs and where the physician suspected pneumonia. Two PHCCs participated. Symptoms and signs as well as degree of suspicion were compared with CXR outcome	Intervention study of patients aged 18 years where the physician suspected pneumonia. Two intervention units and three control units participated. The intervention was to refer for CXR when the physician was not sure of the diagnosis	Prospective observational study of patients aged 18 years where the physician suspected pneumonia after clinical examination. Five PHCCs participated. The physician rated the degree of suspicion before and after CRP results	A register-based study. Data on diagnostic tests performed and antibiotic prescriptions in the management of patients with LRTIs in a whole county between 2006 and 2014, were analysed
Results	Radiographic pneumonia was found in 45%. When physicians were sure of the diagnosis, radiographic pneumonia was found in 88%. CRP level ≥ 50 mg/L was associated with the presence of radiographic pneumonia	There was no difference in the antibiotic prescription rate. High degree of suspicion and high CRP levels were predictors of antibiotic prescription. 24% of the patients with negative CXR were prescribed antibiotics	The degree of suspicion changed in two thirds of cases; most often to a weaker degree and in one third of the cases, there was no longer any suspicion of pneumonia after CRP testing	CRP testing increased in both pneumonia and acute bronchitis. CXR increased in acute bronchitis. The antibiotic prescription rate decreased for acute bronchitis
Conclusion	When the physician is sure of the diagnosis of pneumonia, one can rely on the judgement without ordering CXR	Referral for CXR does not result in lowered antibiotic prescription rates. Physicians do not fully trust negative CXR results in the management of pneumonia in primary care	CRP testing can be helpful in the assessment, particularly to rule out pneumonia.	The fact that the use of CRP and microbiological tests in the diagnostics of LRTIs increased indicates a perceived need for diagnostic tools

PROLOGUE

General practitioners (GPs) meet many patients every day and each consultation involves several decisions. At the end of the consultation, the patient often expects a diagnosis. The scheduled time for an ordinary consultation with a patient with lower respiratory tract infection (LRTI) is usually 15 minutes in Swedish primary care. When I started working in primary care in 2006, most patients with LRTIs were prescribed antibiotics, and to differentiate between acute bronchitis and pneumonia was not that important. Eventually, clinical attention became focused on antibiotic prescription rates as guidelines emerged.

As a resident physician, I sometimes thought it was difficult to interpret the guidelines and to be sure of the diagnosis of pneumonia versus acute bronchitis. Therefore, my scientific work in my training to become a GP was the starting point for my doctoral studies.

Magnus Falk was my supervisor even during my GP training and encouraged me to continue the scientific research. During my PhD studies, I have come to realize how important it is to do pragmatic studies in a clinical context, especially in primary care, where most patients are managed, and where many have more than one disease.

INTRODUCTION

In primary care, diagnosing pneumonia is sometimes challenging, because it may be difficult to differentiate between acute bronchitis and pneumonia. Pneumonia and acute bronchitis are included in lower respiratory tract infections (LRTIs), which is one of the most common reasons for consulting primary care. The diagnosis is often based on signs and symptoms alone. Moreover, the guidelines are different in different countries. Chest X-ray (CXR) is considered the gold standard for the diagnosis of pneumonia, even though it is not completely sensitive or specific, and it is not always available or suitable in primary care. It is important to correctly identify patients with pneumonia, because it is a serious disease that might be lethal, even among young patients. Pneumonia should be treated with antibiotics, whereas acute bronchitis should not because acute bronchitis is considered a self-limiting disease.

For these reasons, it would be of value to find a better diagnostic tool for diagnosing pneumonia in primary care. To do this, we need to investigate the diagnostic value of different clinical and laboratory findings in pneumonia patients, and evaluate the physicians' diagnostic accuracy and compare the degree of suspicion with the gold standard (CXR) (**Paper I**).

The results from Paper I showed that the general practitioner's (GP's) diagnostic accuracy seemed to be good when sure of the diagnosis of pneumonia, therefore a study was done to find out whether the use of CXR could refine the diagnostic process when the physician is not sure of the diagnosis, and if using CXR in this way could decrease the antibiotic prescription rate (**Paper II**).

Point-of-care C-reactive protein (CRP) testing is widely used in Scandinavia when assessing for pneumonia. In **Paper III**, we aimed to find out to what extent the CRP level influences the physician's degree of suspicion of pneumonia.

There are some diagnostic tests and examinations that can be used in the assessment of LRTIs. Because the changes in the use of tests over time and changes in antibiotic prescription patterns were not known, they were evaluated in **Paper IV**.

BACKGROUND

Historical perspective

Sir William Osler (1849–1919), a Canadian medical doctor known as ‘the father of modern medicine’, did research, and early on his career, he also worked as a GP as well as teaching. He soon became a professor and eventually also a pathologist. He is known for his way of looking on pneumonia as a ‘friend of the aged’ because it was a relatively painless way of dying [1]. In his book *The principles and practice of medicine*, he stated that pneumonia caused 76 deaths per 100,000 in the United States in 1890. In 1913, a new technique called antiserum therapy was introduced. It was suggested to reduce mortality from 25% to 7.5% if given early in the course of the disease [2]. Eventually, sulphapyridine, the first antibacterial agent, was introduced in 1939. It got a lot of attention when it was used to cure Winston Churchill in 1942. However, when penicillin was introduced in the early 1940s, sulphapyridine and the efforts to develop vaccines were set aside [3]. However, overuse of antibiotics resulted in emergence of penicillin-resistant strains of *Streptococcus pneumoniae*, the most common cause of pneumonias [4,5]. Thus, vaccines were once again relevant. In the 1970s, the first polysaccharide vaccine against *S. pneumoniae* was developed, but it was not until the late 1990s that it was widely introduced [2]. As vaccines, antibiotics and supportive care have become available, patients recover from pneumonia to a greater extent [6]. Despite this, pneumonia remains the fourth leading cause of death worldwide, and today the mortality in hospitalized patients is 7%–13% [7,8].

Portrait of Sir William Osler, at the age of 70 years. Credit: Wellcome Collection. Attribution 4.0 International (CC BY 4.0)

Lower respiratory tract infections

LRTI is one of the most common reasons for consultation in primary care [9,10]. LRTI is defined as an acute illness for 21 days or less, with the main symptom of a cough, sometimes accompanied by sputum production, chest discomfort, wheeze or dyspnoea [11]. LRTIs consists of acute bronchitis, pneumonia and acute exacerbation of chronic obstructive pulmonary disease (COPD). Acute bronchitis is considered a self-limiting disease and should not generally be treated with antibiotics, whereas pneumonia can be lethal, even among young adults, and antibiotic therapy is therefore recommended [12–14]. It is suggested that acute exacerbation of COPD should be treated with antibiotics in cases of mucopurulent sputum [15]. LRTIs are responsible for a large number of deaths worldwide; almost 2.5 million deaths are caused by LRTIs every year [16].

Community-acquired pneumonia

The annual incidence of community-acquired pneumonia (CAP) varies between 1.5 and 14 per 1000 inhabitants and is dependent on age and how pneumonia is diagnosed [17–20]. Incidence of hospitalization due to CAP is higher among the youngest children and fragile elderly [17,21,22]. Thus, the incidence curve is U-shaped. When using CXR in the assessment, the incidence is lower [23]. A previous study showed that pneumonia was frequently over-diagnosed by GPs when comparing with CXR [24]. The mortality in pneumonia is only 1% among outpatients but increases with age and is higher in hospitalized patients. Moreover, men seem to be more vulnerable than women, and in one study, the incidence was shown to be two-fold higher in men [18,20,25–28].

Sometimes it is a challenge to differentiate between pneumonia and acute bronchitis, because both diseases present with symptoms like cough and fever. Acute exacerbation of COPD can be caused by atypical bacteria or *Haemophilus influenzae*, and therefore the treatment recommendations differ from those for pneumonia.

Pneumonia is categorized into three groups: CAP, nosocomial pneumonia, and ventilator-associated pneumonia. In primary care, most of the pneumonias are community-acquired.

Aetiology of CAP

CAP in primary care is caused by bacteria or viruses [29–31]. Frequency numbers differ greatly between different studies as a result of different microbiological detection methods, different settings, and different age groups [32,33]. Among the viruses causing CAP, influenza viruses, human rhinovirus and respiratory syncytial virus have been shown to be the most frequent causes, and a viral cause has been found in up to 38% of patients with pneumonia in primary care [30,34,35]. During influenza outbreaks, influenza infection is the principle cause of serious CAP requiring hospitalization, often because of complications with secondary bacterial infection [36]. Coinfections are common [30,37]. In 2020, the coronavirus SARS-CoV-2 has caused several viral pneumonias in the world during the Covid-19 pandemic [38]. The most common bacteria causing CAP are *S. pneumoniae*, found in 9%–36%, and *Haemophilus influenzae*, found in 3%–28% of radiographically confirmed pneumonias in primary care [18,30–33,37]. Of these, *S. pneumoniae* is considered the most virulent. Atypical bacteria causing CAP include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* [39,40].

Vaccination

Since 1993, vaccination against *H. influenzae* has been part of the children's national vaccination programme. It has reduced the number of severe childhood pneumonias, epiglottitis and meningitis [41,42]. There are two types of pneumococcal vaccines in Sweden. The one included in the national vaccination programme is a conjugate vaccine and contains 13 serotypes. This vaccine was introduced in the national vaccination programme in 2009 and is preventive for invasive pneumococcal disease (IPD) [43]. The number of invasive pneumococcal infections in small children (under 2 years of age) has decreased since the vaccination against *S. pneumoniae* was introduced [44]. Moreover, there has been a reduction in pneumococcal carriage and a shift towards other serotypes [45,46]. The vaccine has also been shown to reduce IPD overall in all ages [47]. The other vaccine is a polysaccharide vaccine that is recommended for elderly (≥65 years) and at-risk groups. The vaccination has been proven to prevent IPD by 50%–60% in the elderly [48].

Antimicrobial resistance

S. pneumoniae isolates are considered susceptible to penicillin when the minimal inhibitory concentration (MIC) of benzylpenicillin is ≤ 0.06 mg/L, otherwise they are considered penicillin non-susceptible pneumococci [49]. When the MIC is > 1 mg/L, the disease is subject to notification by the Swedish Communicable Diseases Act and must be reported to the public health authority [50]. Because of excessive use of antibiotics, antimicrobial resistance has increased, and today, up to 19% of *S. pneumoniae* isolates in Europe are penicillin resistant [51]. However, the proportion is much lower in Sweden, where only about 1% of the isolates are considered resistant [52]. Multi-drug resistance in pneumococci is defined as resistance to three or more antimicrobial agents. When looking at the resistance pattern of *S. pneumoniae* in the world, up to 30% of the strains are considered multi-drug resistant. Recent antibiotic treatment, extremes of age, alcoholism, medical comorbidities, immunosuppressive illness or treatment, and exposure to a child in a day-care centre are some risk factors for drug-resistant *S. pneumoniae* that have been identified [53].

Outpatient use of antibiotics varies between countries, and there is a correlation between antibiotic resistance and outpatient antibiotic use in Europe [54]. Thus, it seems important to keep the number of antibiotic prescriptions low. However, some studies indicate overuse of antibiotics for respiratory tract infections [55,56]. In Sweden, the antibiotic prescription rate is low compared with countries in southern Europe, such as France, Greece and Spain. Some countries, for example, the Netherlands prescribe even less antibiotics [54]. However, antibiotic prescriptions have decreased for respiratory tract infections in Sweden [57,58].

The mechanism of β -lactam resistance in *S. pneumoniae* consists of multiple alterations in several penicillin-binding proteins (PBPs) in the cell wall. These alterations result in a decrease in affinity to β -lactams, and the MIC increases [59,60].

In the late 1980s, there was an increase in *S. pneumoniae* with reduced sensitivity to penicillin. This was the starting point for an increase in preventive work. The Swedish strategic programme against antibiotic resistance (Strama) was founded in 1995. It was formed as a voluntary

network to highlight the increasing problem of antibiotic-resistant bacteria and to increase awareness. Since then, there has been a correlated decline in antibiotic use, with no observed negative effects [61,62].

Strategies aiming at reducing resistance to antibiotics include increased knowledge by enhanced monitoring, strong prevention, responsible use of antibiotics and increased knowledge in society [63].

Proportion of penicillin-resistant isolates of *S. pneumoniae* in Europe in 2018. Dataset provided by the European Centre for Disease Prevention and Control based on data provided by the World Health Organization and Ministries of Health from the affected countries.

Clinical decision making

Clinical diagnosis is based on anamnestic information (history), clinical examination and sometimes laboratory findings. Physicians sometimes use the overall “clinical impression”, which is an intuitive approach, whereby the physician assesses the different signs and symptoms, and the approach is based on pattern recognition. The overall clinical impression has been found to be an accurate diagnostic test for CAP [64,65]. But what is behind the overall clinical expression? This is not known. The overall clinical expression differs from the evidence-based practical approach that is used in clinical decision rules (CDRs) and guidelines. Several studies have aimed to identify a CDR for pneumonia, but with varying results [65–73]. Progression of symptoms over time has been suggested as a factor to predict CAP in primary care [74].

CDRs are not always used to the desired extent in clinical practice because they are sometimes perceived as cumbersome and not developed for the clinical context [75]. Furthermore, the physician’s preconceptions of diagnosis and treatment might play a role in the assessment and may reduce adherence to CDRs [76].

Auscultation of the lungs

The stethoscope has been a central part of examining the thorax for two centuries and has come to be a symbol of physicians. Photographs of physicians often show them with a stethoscope. Patients consulting primary care due to fever and cough expect lung auscultation to be performed. But what does it add? Studies have shown that lung auscultation is not enough to confirm, or exclude, the diagnosis of pneumonia, and there is wide interobserver variability [77,78]. Moreover, adventitious lung sounds have been shown to be present in healthy people [79].

Imaging

Chest X-ray

CXR is considered the gold standard for the diagnosis of pneumonia despite its insufficiency regarding sensitivity and specificity. Some infiltrates will not be detected early in the course of pneumonia, but when reinvestigating 48 hours later, they might show up according to progression of the disease [80]. Despite its low dose of radiation, CXR is not used routinely in Swedish primary care in the assessment of pneumonia because it is not always available or suitable in primary care [81–83]. The patient's age and decreased breath sounds on auscultation have been associated with ordering CXR in the assessment [84]. The imaging might be masked by inflammatory complications, such as effusions, pulmonary oedema, acute respiratory distress syndrome, or indistinct initial findings. Moreover, there is diagnostic overlap regarding the cause and the different radiologic patterns of pneumonia. However, when the pneumonia is of viral origin, the infiltrates are more often bilateral and multi-lobular [85,86].

High-resolution computed tomography

High-resolution computed tomography (HRCT) has been shown to detect more infiltrates than CXR in cases of CAP [87–89]. It has been suggested to be useful for early diagnosis and treatment of patients with a clinical diagnosis in hospital care [90]. However, the relevance of the findings on HRCT in primary care is unclear, because an infiltrate on HRCT but not on CXR does not necessarily indicate a bacterial infection requiring antibiotic treatment and thus risks overdiagnosis. Moreover, HRCT is not feasible in the diagnostics of pneumonia in primary care due to its higher costs and limited availability.

Lung ultrasonography

Point-of-care lung ultrasonography (LU) has been evaluated and suggested to be superior to CXR in diagnosing pneumonia [91]. The examination does not lead to any radiation exposure and can be performed and interpreted at the clinic in real time. However, there are some limitations. For example, LU requires an experienced physician to perform and interpret the examination, and it is time consuming. It is also difficult to compare over time, and the results might vary between practitioners. Moreover, the equipment is expensive [92]. Today, point-of care LU is not available in primary care and when used in emergency units, consolidation by confirming with CXR is recommended [93]. Therefore, it is currently not a useful method in primary care.

Point-of-care tests

Point-of-care testing (POCT), also called near-patient testing, is when a test is performed and analysed within the consultation time. There are several POCTs used in primary care; for example, erythrocyte sedimentation rate, white blood cell count (WBC) and C-reactive protein (CRP). All these tests have been shown to depend on the duration of illness [94]. Further, WBC has been suggested to be helpful when differentiating bacterial and atypical or viral pneumonia [95]. Several studies have also evaluated procalcitonin (PCT) as a predictor of pneumonia and a possible POCT. PCT is a precursor to the hormone calcitonin. It is synthesized in the thyroid, in the neuroendocrine cells in the lung and in the intestine. Production increases in response to inflammation and particularly in response to bacterial infection. PCT is suggested to be useful in the care of pre-septic patients in emergency departments, but the results are inconsistent in trials concerning its added benefit in the diagnostics of CAP [96,97]. However, PCT has been shown to be of limited added value for the diagnostics of pneumonia in primary care [70].

CRP

In 1930, Tillet and Francis identified a substance in the serum of patients with pneumococcal disease that interacted with Polysaccharide C in the capsule of *S. pneumoniae* [98]. This substance, i.e. CRP, is synthesized by hepatocytes mainly in response to tissue damage, for example, by infection and/or inflammation [99].

In CAP caused by *S. pneumoniae*, a significant increase in CRP is often seen, whereas viral pneumonias or pneumonia of atypical bacterial origin is associated with lower CRP levels. However, a previous study showed that in patients with non-severe CAP, CRP could not differentiate between viral and bacterial causes [100].

CRP increases rapidly during 6–8 hours and reaches a peak after 48 hours [101]. Therefore, symptom duration is an important factor when interpreting CRP results [94]. In Scandinavia, CRP was introduced in primary care in the 1990s and is now available as a finger prick POCT at most primary health care centres (PHCCs) in Sweden [102].

The use of CRP to assess respiratory tract infections has been questioned, because misinterpretation has resulted in overprescribing of antibiotics for viral diseases, and antibiotic prescriptions have not been shown to decrease in low prescribing countries [103,104]. However, CRP testing has also been shown to decrease antibiotic prescription rates and is sometimes used as a decision aid to determine whether or not to request a CXR [105–110]. Further, CRP has been suggested as the preferred biomarker, alone and as part of a CDR for diagnosis of CAP in primary care [70,111,112].

Guidelines

Different countries in the world, including European countries, have different guidelines concerning how to assess pneumonia at the initial judgement in primary care. For example, CRP is recommended in the initial judgement of pneumonia according to some guidelines but not others. Further, the Infectious Diseases Society of America and the American Thoracic Society's treatment guidelines require radiographic confirmation in contrast to European guidelines. [11,113–118]. The assessment of CAP differs between countries, and in Scandinavia, CRP is widely used, whereas CXR is more often used in, for example, Spain [23,119]. The Swedish guideline suggests that pneumonia should be suspected in the case of a generally sick patient with symptoms such as fever, cough, recent-onset fatigue and/or lateral chest pain, particularly in combination with typical clinical findings such as focally depressed, or altered, lung sounds, dullness on percussion, tachypnea or tachycardia. The initial judgement does not include CRP testing or CXR examination. When the diagnosis of LRTI is unclear after clinical examination, CRP testing might be considered. CRP should then be assessed in relation to the symptom duration.

It is suggested that if:

- CRP >100 mg/L and there is a clinical picture of pneumonia, antibiotics should be considered;
- CRP <20 mg/L after 24 hours of symptom duration, pneumonia can probably be excluded;
- CRP >50 mg/L and symptoms of more than 1 week, indicates pneumonia and antibiotics should be considered.

If the physician is still in doubt after clinical examination, the recommendation is either watchful waiting, consideration to refer for CXR or delayed antibiotic prescription [114].

During the pandemic of Covid-19, the assessment has changed and the National Institute for Health and Care Excellence (NICE) rapidly withdrew their guideline on diagnosing and managing of CAP until further notice, and replaced it with an interim Covid-19 guideline partly adapted to remote assessment [120].

Treatment

Treatment recommendations for pneumonia also differ between countries. Phenoxymethylpenicillin is effective against *Streptococcus* species, and because *S. pneumoniae* is considered the most virulent of the commonest causes of CAP, phenoxymethylpenicillin is the drug of choice in Sweden. In the case of treatment failure or allergy, doxycycline is recommended [114]. The Infectious Diseases Society of America suggests a macrolide or doxycycline in the treatment of outpatients with pneumonia, whereas the European Respiratory Society and the British Thoracic Society recommend amoxicillin or tetracycline as first choice [11,115,121].

As mentioned above, acute bronchitis is often a self-limiting disease and antibiotic treatment is not beneficial [122].

Delayed antibiotic prescription

This is a way to reduce inappropriate use of antibiotics. It is defined as a prescription of antibiotics for the patient to use if the symptoms deteriorate or persist for several days after the visit [123]. Delayed prescription has been shown to reduce antibiotic consumption and, in addition, enhance patient satisfaction and empowerment, reduce re-consultations and provide a safety net [124,125]. On the other hand, it may result in storage of antibiotics for later use, medicalization of minor illness and lower satisfaction levels [123].

AIMS OF THE THESIS

Overall aim

To study factors associated with clinical assessment of pneumonia in primary care and to investigate if diagnostics of pneumonia in primary care can be improved, in order to reduce inappropriate prescription of antibiotics.

Specific objectives

1. To investigate the diagnostic value of different clinical and laboratory findings in pneumonia and to explore the association between the doctor's degree of suspicion of pneumonia and CXR results and to evaluate whether CXR should be used routinely in primary care, when available. (**Paper I**)
2. To explore the benefit of using CXR when the physician is not sure of the diagnosis of pneumonia, and if using it this way, results in a lower antibiotic prescription rate. (**Paper II**)
3. To investigate to what extent the physician's degree of suspicion is affected by the CRP level when community-acquired pneumonia is suspected in primary care. (**Paper III**)
4. To calculate the proportion of diagnostic tests in the management of LRTIs in a low-antibiotic-prescribing country, and to evaluate if the use of tests has changed over time. The secondary aim was to investigate if the prescription pattern changed over time. (**Paper IV**)

MATERIALS AND METHODS

Table 2

	I	II	III	IV
Design	Prospective observational study	Intervention study	Prospective observational study	Retrospective register-based study
Study population	Patients aged 18 years, presenting with LRTIs, where the physician suspected pneumonia. Included at two PHCCs in Sweden ($n = 103$)	Patients aged 18 years, presenting with LRTIs, where the physician suspected pneumonia. Included at two intervention units ($n = 104$) and three control units ($n = 81$)	Patients aged 18 years, presenting with LRTIs, where the physician suspected pneumonia. Included at five PHCCs ($n = 266$)	Patients 18–79 years, who consulted their PHCC, in the county council of Kronoberg and were diagnosed with pneumonia, acute bronchitis or cough ($n = 54,229$)
Data collection period	2011–2014	2015–2017 (–19)	2015–2017	2006–2014
Data analyses	Means were compared using the t test. Comparison between proportions were performed with the chi-squared test. A logistic regression model was performed to explore the association of different variables with positive CXR. The model was supplemented by a stepwise backward elimination. Linear-by linear association was used to evaluate the ordinal trend in degree of suspicion in relation to CXR outcome	Medians were compared using the Mann-Whitney U test. Comparison between proportions in categorical variables were performed with the chi-squared test. A logistic regression was performed to explore which factors correlated with the propensity to prescribe antibiotics. Nagelkerke R^2 and area under curve were estimated for measures of internal validity of the model	Comparison between proportions were performed with the chi-squared test. Differences in CRP between different degrees of suspicion were calculated with the Kruskal Wallis test. The Mann-Whitney U test was used to identify any significant differences between two groups. A logistic regression was performed to explore the association of different variables with the doctor's degree of suspicion	Calculations of descriptive data. Comparisons between proportions were performed with the chi-squared test. A binary logistic regression model was used to analyse any significant change over time, using the first year as reference. When adjusting for confounders, a multiple logistic regression model was used

Study populations

The doctor's suspicion of pneumonia as a predictor in the assessment of pneumonia

Paper I

Two PHCCs in the south of Sweden participated in the study between 1 September 2011 and 31 December 2014. In total, 103 patients were included. Patients, aged 18 years, consulting primary care with symptoms of LRTI for more than 24 hours and where the primary care physician suspected pneumonia after clinical examination, were included consecutively. Exclusion criteria were known COPD, self-reported ongoing pregnancy and living in a nursing home.

Three patients were excluded. One due to missing CXR examination. The other two had been diagnosed with pneumonia and treated with antibiotics recently and thereby the degree of suspicion and CXR result could be difficult to interpret.

Papers II and III

These papers derived from the same study population. Four PHCCs in the south of Sweden participated in the recruitment of patients initially. Because the inclusion rate appeared to be lower than expected, one more PHCC was asked to participate after a year and was allowed inclusion for the same time. The study continued for 28 months for **Paper II** and ended after 15 months for **Paper III**. The inclusion and exclusion criteria were the same as in **Paper I**, with the exception of **Paper III**, for which inclusion was made at an earlier stage, i.e. when the physician had some degree of suspicion of pneumonia before CRP testing.

Paper II is an intervention study; two of the PHCCs served as intervention units and three as control units. In total, 104 patients were recruited to the intervention group and 81 to the control group. The total number of

patients recruited in **Paper III** was 266. Due to missing information on degree of suspicion, one patient was excluded.

The use of diagnostic tests and antibiotic prescriptions over time

Paper IV

The register used in this study is based on data from electronic health records (EHRs) from every PHCC in Kronoberg county in the south east of Sweden between 2006 and 2014. In total, 33 PHCCs and three out-of-hours services were included. Data from doctor visits by patients aged 18–79 years and with the diagnoses of acute bronchitis, pneumonia, or the symptom diagnosis cough were analysed. One sickness episode was defined as 6 weeks. Therefore, if several contacts, by the same patient, occurred within 6 weeks and with the same diagnosis, they were considered as one contact, and the first antibiotic prescribed was analysed.

The reason why patients older than 79 years were not included was that several in this age group have dose-dispensed medications. Since dose-dispensed medicines are administered through another computer system without connection to the EHRs they are not eligible for analyses.

Data collection/measurements

Papers I–III

Patients were included consecutively when consulting primary care and the physician had some degree of suspicion of pneumonia after clinical examination. Inclusion occurred during regular working hours.

Anamnestic information and findings at the clinical examination were documented in case report forms (CRFs) (**Table 3**). WBCs were drawn from patients in **Paper I**. CRP levels were drawn from all patients, and laboratory results were documented in the CRF. The physicians were also asked to estimate, and document, the degree of suspicion of pneumonia into one of three degrees: unsure, quite sure, or sure. In **Paper I**, this was done after clinical examination and laboratory testing, and thereafter, all patients were referred for CXR. The physicians were free to prescribe antibiotics before or after the result of the CXR examination was available. In **Papers II** and **III**, the physician judged the degree of suspicion before and after the CRP level was known, then with the added option of ‘no longer pneumonia’.

Patients referred for CXR were examined within 48 hours. The radiologists were not blinded to anamnestic or clinical information and were aware of the inquiry. The radiologist on duty gave a preliminary statement and the examinations were then reviewed once more by a second radiologist who gave a definitive statement, according to standard clinical routine.

Table 3 Anamnestic, clinical and laboratory findings examined in **Papers I–III**

	Paper I	Paper II	Paper III
Gender	x	x	x
Age	x	x	x
Current smoker	x	x	x
Symptom duration		x	x
Focal chest sounds		x	x
-Rales	x		
-Crackles	x		
-Decreased breath sounds	x		
Dullness to percussion	x		
Respiratory rate	x		
Pulse	x		
Body temperature	x	x	x
Antipyretics		x	x
Blood oxygen saturation	x		
CRP	x	x	x
WBC	x		
Degree of suspicion	x	x	x
-Before CRP testing			x
-After CRP testing	x	x	x

The intervention in **Paper II** was to refer all patients for CXR when the physician was 'unsure' or 'quite sure' after clinical examination and CRP testing. If antibiotics were required, they were prescribed after the CXR result. The decision on treatment was based on the first answer that arrived, i.e. sometimes a preliminary answer and sometimes a definitive answer. Patients at the control units were assessed according to the clinical routine after CRP testing. The antibiotic prescribing rate was compared between the groups.

In **Paper III** the change in degree of suspicion of pneumonia after CRP testing was evaluated.

Paper IV

The data were collected from EHRs. All data were extracted on one occasion and included information on patients diagnosed with acute bronchitis, pneumonia, or cough after consulting primary care. To identify the diagnosis, the Swedish primary health care version of the ICD-10 was used.

Data included information on gender, age at the consultation, PHCC, diagnoses, CRP tests performed, microbiological tests, radiology, results of the tests performed, whether any antibiotics were prescribed and, in those cases, which antibiotic was prescribed.

Ethical considerations

Participation was voluntary, and there was a possibility to withdraw participation at any time. All the participants in the three prospective studies gave written informed consent to participate. Ethical approval was obtained for each study. The first two studies differ from ordinary routine regarding the number of patients exposed to CXR. Therefore, children were not included, and known ongoing pregnancy was an exclusion criterion. The dose of radiation that the patient is exposed to during one CXR examination is low, and the risks are considered to be small. CXR examination is painless and non-invasive and will not cause the patient any discomfort. When imaging is used, there is always a risk that incidental findings will appear, which might result in further investigations. This may cause concern for the patient. There is also a risk that some pneumonias will not be detected at the CXR examination. The inclusion criterion of symptom

duration of more than 24 hours will diminish the risk of missing early pneumonias. Some studies have indicated higher sensitivity when using HRCT in the diagnostics. However, using HRCT would not be suitable either practically or socioeconomically.

For patients, prescribers and health care centres, confidentiality in the register was ensured by one-way encrypted ID numbers. Because the patients' data were anonymized, the integrity is considered to be high, and the risk of patients, or prescribers being identified during data processing is negligible.

All data are presented at group level in a way that no individual can be identified.

The studies were expected to contribute valuable knowledge for future development and optimization of the management of pneumonia in primary care.

RESULTS

The doctor's degree of suspicion as a predictor of pneumonia (Paper I)

Outcomes of CRP tests, CXRs and antibiotic prescriptions in relation to clinical judgements by means of degree of suspicion of pneumonia for **Paper I-III** is shown in **Table 4**.

Of the 100 patients eligible for analyses in **Paper I**, 45% with suspected pneumonia had pneumonia on CXR.

We found that the physician's degree of suspicion was associated with the presence of a new consolidation on CXR as seen in **Figure 1**. When the physician was sure of the diagnosis of pneumonia, CXR was positive in 88% of cases.

Figure 1 Degree of suspicion of pneumonia in primary care and outcome of chest X-ray (CXR)

Table 4 Outcomes of CRP tests, chest X-rays (CXR) and prescription of antibiotics in relation to clinical judgements by means of degree of suspicion of pneumonia after CRP testing

	n			CRP (mg/L), median (interquartiles)		Positive CXR, n (%)	Antibiotics prescribed, n (%)		Antibiotics prescribed when CXR negative, n (%)
	Paper I	Paper II (control/inter-vention)	Paper III	Paper I	Paper III		Paper I	Paper II (control/inter-vention)	
Total	103	81/104	266	61 (22, 107)	37 (11, 84)	45 (45)	76 (76)	62/71 (77/69)	53/100
Degree of suspicion:									
-No longer pneumonia			72		11 (5, 20)				
-Unsure	43	22/41	64	31 (10, 65)	23 (9, 51)	12 (28)	23 (54)	7/17 (32/42)	3 (9)
-Quite sure	40	30/31	65	72 (33, 107)	63 (37, 101)	18 (45)	37 (93)	26/27 (87/79)	5(33)
-Sure	16	29/28	55	101 (89, 152)	112 (70, 160)	14 (88)	15 (94)	29/27 (100/96)	5(83)

CRP ≥ 50 mg/L associated strongly with positive CXR (**Figure 2**), and the significance remained after adjusting for covariates (odds ratio, 11; 95% confidence interval, 3.0–39). Being a current smoker was negatively associated with presence of pneumonia on CXR. None of the other independent variables remained associated with CXR findings after adjusting for covariates (**Table 5**). When performing a logistic regression with step-wise backward elimination, the results were similar (**Table 5a**). Positive predictive value (PPV) was higher when the degree of suspicion was ‘sure’ than for CRP ≥ 50 mg/L (**Table 6**).

Figure 2 CRP in relation to outcome of CXR. Positive CXR is defined as radiographic pneumonia.

Table 5 Association between different diagnostic variables including clinical findings, laboratory findings and anamnestic data, and radiographic pneumonia in primary care showing the crude and adjusted odds ratio (OR) for having radiographic pneumonia: enter model

Diagnostic variable	Crude					Adjusted	
	Total (n = 100), n (%)	Positive CXR (n = 45), n (%)	Negative CXR (n = 55), n (%)	p value	OR (95% CI)	p value	OR (95% CI)
Men	45 (45)	17 (38)	28 (51)	0.19	0.59 (0.26-1.3)	0.28	0.52 (0.16-1.7)
Age ≥65 years*	34 (34)	18 (40)	16 (29)	0.25	1.6 (0.71-3.7)	0.66	1.3 (0.41-4.1)
Current smoker	12 (12)	3 (6.7)	9 (17)	0.14**	0.35 (0.09-1.4)	0.036	0.11 (0.014-0.86)
Lateralized chest pain	17 (18)	7 (16)	10 (19)	0.74	0.84 (0.29-2.4)	0.90	0.90 (0.18-4.7)
Crackles	48 (48)	21 (46)	27 (49)	0.81	0.91 (0.41-2.0)	0.92	1.1 (0.33-3.4)
Rales	23 (23)	15 (33)	8 (15)	0.026	2.9 (1.1-7.8)	0.12	3.2 (0.76-13)
Decreased breath sounds	23 (23)	9 (21)	14 (26)	0.56	0.75 (0.29-1.9)	0.78	0.80 (0.17-3.8)
Dullness to percussion	15 (16)	5 (12)	10 (19)	0.35	0.58 (0.18-1.8)	0.26	0.32 (0.045-2.3)
Body temperature (≥38°C)	21 (21)	15 (33)	6 (11)	0.007	4.0 (1.4-11.4)	0.13	3.3 (0.71-15)
Tachypnoea (≥20 breaths/min)	55 (57)	26 (61)	29 (55)	0.57	1.3 (0.56-2.9)	0.68	0.77 (0.22-2.7)
Tachycardia (≥100 beats/min)	28 (29)	13 (30)	15 (28)	0.85	1.1 (0.45-2.6)	0.91	1.08 (0.29-4.0)
Desaturation (<95%)	26 (26)	14 (31)	12 (22)	0.29	1.6 (0.66-4.0)	0.77	1.2 (0.32-4.7)
CRP (≥50 mg/L)	57 (57)	37 (82)	20 (36)	<0.001	8.1 (3.2-21)	<0.001	11 (3.0-39)
Leucocytosis (≥15 x 10 ⁹ /L)	12 (12)	7 (16)	5 (9.3)	0.32	1.9 (0.5-6.3)	0.98	1.0 (0.16-6.5)

Data missing was <5% for all variables. Chi-squared test. ORs were calculated using the Mantel-Haenzel equation. Multiple logistic regression model. All variables in the table. Nagelkerke R², 0.45; area under the curve, 0.84 (0.76–0.93).

*Not in article. **Fisher's exact test.

Table 5a. Association between clinical findings and positive chest X-ray

	<i>p</i> value	OR (95% CI)
Rales	0.07	3.2 (0.91-11)
Current smoker	0.01	0.11 (0.18-0.64)
CRP ≥ 50 mg/L	<0.001	11 (3.8-37)

Last step in the multiple logistic regression, stepwise backward elimination, Wald. Nagelkerke R^2 , 0.37; area under the curve, 0.82 (95% CI, 0.73-0.90).

Table 6 Positive predictive value (PPV) and negative predictive value (NPV) for CRP and when the degree of suspicion was sure for the diagnosis of pneumonia

	PPV (%)	NPV (%)
CRP ≥ 50 mg/L	65	81
Sure	88	62

Physicians do not fully trust CXR results (Paper II)

In the intervention study, the overall antibiotic prescription rate was 72% and did not differ between the intervention and control groups. CRP level and degree of suspicion were found to be the most important predictors for antibiotic prescription (**Table 7**). We also noted that even when CXR was negative, 24% of the patients were prescribed antibiotics. Moreover, the most important factor for antibiotic prescription in those cases was the physician's degree of suspicion (**Table 8**).

In the control group, longer symptom duration was associated with referral for CXR ($p = 0.029$). The frequency of CXR was 26% in the control group compared with 85% in the intervention group, indicating adherence to the intervention.

Table 7 Factors correlating to the propensity to be prescribed antibiotics when community-acquired pneumonia is suspected: crude and adjusted data (enter model)

	Univariable logistic regression			Multivariable logistic regression (n = 166)*	
	n	p value	OR (95% CI)	p value	OR (95% CI)
Intervention (1) versus control (0)	184	0.25	0.68 (0.35–1.3)	0.81	1.1 (0.43–3.0)
Male	184	0.36	1.4 (0.71–2.6)	0.41	1.5 (0.56–3.8)
Age (per year)	184	0.59	1.0 (0.99–1.0)	0.50	0.99 (0.97–1.0)
Symptom duration (per day)	182	0.04	0.96 (0.93–1.0)	0.40	0.97 (0.90–1.0)
Body temperature (per °C)	181	0.03	1.7 (1.1–2.8)	0.80	1.1 (0.54–2.2)
Smoking	179	0.38	1.6 (0.56–4.6)	0.56	1.6 (0.35–7.0)
Antipyretics	174	0.71	0.88 (0.45–1.7)	0.26	1.8 (0.64–5.0)
Abnormal focal chest sounds	182	0.68	0.87 (0.45–1.7)	0.93	0.96 (0.34–2.7)
Degree of suspicion**	184	<0.001	8.5 (4.4–16.5)	<0.001	6.7 (2.7–16.9)
CRP (per 10 mg/L)	184	<0.001	1.4 (1.2–1.5)	0.024	1.2 (1.03–1.4)

*Nagelkerke R², 0.52; area under the curve, 0.89 (95% CI, 0.84–0.94).

**The physicians' suspicion of pneumonia: unsure, quite sure or sure.

Table 8. Factors correlating to the propensity to be prescribed antibiotics when chest X-ray is negative in patients when community-acquired pneumonia is suspected in primary care: crude and adjusted data (enter model)

	Univariable logistic regression		Multivariable logistic regression (n = 51)*	
	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)
Intervention (1) versus control (0)	0.13	0.36 (0.099–1.4)	0.18	0.27 (0.38–1.9)
Male	0.041	4.4 (1.1–19)	0.29	3.5 (0.35–34)
Age (per year)	0.015	1.1 (1.01–1.1)	0.54	1.0 (0.99–1.0)
Symptom duration (per day)	0.50	0.97 (0.90–1.1)	0.64	1.0 (0.92–1.2)
Body temperature (per °C)	0.18	2.1 (0.71–6.1)	0.49	0.53 (0.89–3.2)
Antipyretics	0.42	1.7 (0.46–6.6)	0.67	1.7 (0.16–18)
Abnormal focal chest sounds	0.32	1.9 (0.54–6.7)	0.22	3.9 (0.44–35)
Degree of suspicion**	0.001	6.6 (2.2–20)	0.02	5.8 (1.3–26)
CRP (per 10 mg/L)	0.001	1.4 (1.1–1.6)	0.21	1.2 (0.9–1.6)

*Nagelkerke R², 0.60; area under the curve, 0.91 (95% CI, 0.81–1.0).

**The physicians' suspicion of pneumonia: unsure, quite sure or sure.

CRP influences the doctor’s degree of suspicion of pneumonia (Paper III)

In 69% of the cases, the physicians changed their degree of suspicion after the CRP result. The degree of suspicion was lowered in 40% and strengthened in 29% (**Figure 2**).

Figure 2 Distribution and shift in degree of suspicion before and after the CRP results. The narrow bars represent the shift in degree of suspicion.

Abnormal chest sounds and body temperature $\geq 38^{\circ}\text{C}$ were strongly associated with higher degree of suspicion before CRP testing (**Table 9**). And abnormal chest sounds and CRP ≥ 50 mg/L appeared to be correlated with sustained suspicion of pneumonia after CRP testing (**Table 10**).

Table 9 Odds ratios of strong suspicion (quite sure or sure) of pneumonia before CRP testing: multivariate logistic regression enter model

Adjusted logistic regression (N = 235, missing 30)		
	<i>p</i> value	Odds ratio (95% CI)
Female	0.36	1.3 (0.71-2.6)
Age ≥ 65 years	0.14	0.59 (0.29-1.2)
Symptom duration	0.38	0.98 (0.93-1.0)
Current smoker	0.29	1.8 (0.59-5.6)
Body temperature $\geq 38^{\circ}\text{C}$	0.042	2.3 (1.0-5.1))
Abnormal chest sounds	<0.001	13 (6.4-242)
Intake of antipyretics	0.78	0.91 (0.47-1.8)

Nagelkerke R^2 , 0.372; area under the curve, 0.811 (95% CI, 0.75–0.87).

Table 10 Odds ratios of degree of suspicion of pneumonia remaining after CRP testing: multivariable logistic regression (enter model)

Adjusted logistic regression (N = 231, missing 34)		
	<i>p</i> value	Odds ratio (95%CI)
Female	0.15	1.8 (0.81-4.2)
Age >65 years	0.057	0.38 (0.14–1.07)
Symptom duration	0.39	1.0 (0.98–1.1)
Current smoker	0.73	1.3 (0.33-4.9)
Body temperature $\geq 38^{\circ}\text{C}$	0.99	0.29 (0.29-3.4)
Abnormal chest sounds	<0.001	16 (6.4-38)
Intake of antipyretics	0.89	0.93 (0.39-2.2)
CRP ≥ 50 mg/L	<0.001	79 (19-335)

Nagelkerke R^2 , 0.571; area under the curve, 0.904 (95% CI, 0.86–0.94).

The CRP result was found to be strongly associated with the degree of suspicion after testing, as shown in **Figure 3**.

Figure 3. Median CRP levels for the different degrees of suspicion after CRP testing ($p < 0.001$), Kruskal Wallis test. Circles and the asterisk represent outliers and extreme outliers, respectively (box and whisker plot).

Use of diagnostic tests increases in the diagnosis of LRTI in primary care (Paper IV)

In total 54,229 sickness episodes were eligible for analyses in the register after excluding patients older than 79 years and revisits within 6 weeks (**Figure 4**). When analysing the whole material, diagnostic testing was shown to have increased during the study period (**Table 11**).

Figure 4. Flowchart of the inclusion and exclusion process.

Table 11 Change in frequency of diagnostic testing for pneumonia, acute bronchitis and cough in primary care between 2006 and 2014

	Frequency 2006–2014 (%)	<i>p</i> value	OR (95% CI)
CRP	55-62	<0.001	1.3 (1.2–1.4)
CXR*	6.8-9.4	<0.001	1.5 (1.3–1.7)
Microbiological testing*	2.2-4.2	<0.001	2.3 (1.8–2.8)

*Data were not available between 2006 and 2007 and are from 2008.

For pneumonia, the change in diagnostic testing over time is shown in **Figure 5**. CRP testing was found to increase for both acute bronchitis and pneumonia (13% versus 17%) during the study period. CRP testing was used more often in the diagnosis of pneumonia (71%) compared with acute bronchitis (62%) ($p < 0.001$). When pneumonia was diagnosed, the median CRP level was 62 mg/L (interquartiles 27 and 107 mg/L) compared with 11 mg/L (interquartiles 8 and 29 mg/L) in acute bronchitis.

For acute bronchitis, the use of CXR increased from 3% to 5% ($p < 0.001$) but was stable for the diagnosis of pneumonia at 12% of cases.

Use of microbiological tests was low but increased during the study period for the diagnosis of pneumonia. The most common microbiological test performed was polymerase chain reaction (PCR) for *M. pneumoniae* (67%).

Diagnostic tests in pneumonia

Figure 5: Proportion of patients aged 18–79 years with pneumonia in primary care where CRP, CXR or microbiological tests were used in the diagnostic process, shown over time. Data for CXR and microbiological tests are lacking for 2006 and 2007.

Antibiotic prescriptions decreased for acute bronchitis

Antibiotic prescriptions for acute bronchitis decreased significantly during the study period from 74% to 41% ($p < 0.001$). The prescription rate for pneumonia was 84% and did not change over time (**Figure 6**). Prescriptions for phenoxymethylpenicillin for pneumonia increased over time, but decreased for amoxicillin and erythromycin ($p < 0.001$). However, prescription rate for doxycycline was 37% for pneumonia. When narrow-spectrum antibiotics (phenoxymethylpenicillin or amoxicillin) were prescribed for pneumonia, the median CRP was 70 mg/L compared with 50 mg/L when broad-spectrum antibiotics (doxycycline or erythromycin) were prescribed ($p < 0.001$).

Doxycycline was the most prescribed antibiotic for acute bronchitis and the proportion did not change over time (**Figure 7**). The period prevalence of pneumonia peaked in 2011–2012 but was otherwise at a stable level (**Table 12**).

Proportion treated with antibiotics

Figure 6 Proportions of patients aged 18–79 years with lower respiratory tract infections and coughs treated with any antibiotics in primary care.

Figure 7. Distribution of antibiotic prescriptions for pneumonia and acute bronchitis over time in patients aged 18–79 years in primary care.

Table 12. Prevalence of pneumonia and acute bronchitis and antibiotics prescribed in patients aged 18–79 years in primary care presented as number per 1000 inhabitants in the corresponding age group for each year. Confidence intervals within brackets.

	2006	2007	2008	2009	2010	2011	2012	2013	2014
Pneumonia	9.7 (9.1–10)	10.3 (9.8–11)	8.6 (8.1–9.1)	10.1 (9.8–11)	10.9 (10–11)	15.8 (15–16)	14.0 (13–15)	11.3 (11–12)	10.5 (10–11)
- Antibiotics	8.2	8.7	6.9	8.7	9.1	13.5	11.8	9.5	9.1
Acute bron- chitis	25.2 (24–26)	26.5 (26–27)	23.0 (22–24)	20.7 (20–22)	21.8 (21–23)	26.9 (26–28)	25.7 (25–27)	23.0 (22–24)	20.7 (20–21)
- Antibiotics	18.6	19.1	15.3	12.5	12.0	14.3	12.9	10.5	8.5

DISCUSSION

Main findings

The doctor's degree of suspicion as a predictor of pneumonia

We found that the doctor's degree of suspicion works well as a predictor of pneumonia, which means that when the physician is sure of the diagnosis after examination, no further investigation is needed and antibiotics can be prescribed on reliable grounds.

Physicians were sure in 16%–36% of cases, and hence had a lower degree of suspicion of pneumonia in most cases, indicating a need for further diagnostic aid.

Except for CRP, none of the other clinical, laboratory or anamnestic information investigated correlated with radiographic pneumonia. Attempts to find a decision rule for pneumonia in primary care are many, and the results do not conform.

In clinical praxis, this finding could contribute to strengthen the physicians' confidence in the diagnosis and further investigations seems irrelevant when sure of the diagnosis of pneumonia.

Extended use of CXR does not result in decreased rates of antibiotic prescription

The intervention to refer for CXR when unsure or quite sure of the diagnosis did not result in a decrease in the rate of antibiotic prescription. Even if we assumed that all those with a negative CXR were not prescribed an antibiotic, the difference was not statistically significant. The high frequency of CXRs in the control group might explain the lack of a difference. Another interesting finding was that, in the control group, longer symptom duration was more common when a decision to refer for CXR was made, indicating use of CXR as a diagnostic tool in cases of uncertainty.

Physicians do not fully trust CXR results

When introducing an intervention aiming to improve diagnostic accuracy, it was found that CXR was already used in 26% of cases, which is twice as much as in the register study (**Paper IV**). Further, physicians did not fully trust a negative CXR outcome as reflected in terms of antibiotic prescription rates. When pneumonia was suspected, antibiotics were prescribed in one in four cases of a negative CXR (**Paper II**). Moreover, in **Paper I**, the rate of antibiotic prescriptions when CXR was negative was even higher (58%). However, the design of that study allowed the physician to prescribe antibiotics before the result of CXR was known. Hence, the data are not comparable. A predictor of antibiotic prescription when CXR was negative was the degree of suspicion, indicating a higher confidence in clinical judgement than a negative CXR result.

The finding that prescription of antibiotics occurred to a surprisingly high degree in patients with a negative CXR is interesting. Several factors might contribute. It has been suggested that prescription of antibiotics depends on the physician's prescribing behaviour more than on the clinical picture [126]. Further, the knowledge that CXR is not a perfect reference standard, and that some infiltrates will not show, might influence the doctor's propensity to prescribe antibiotics.

Lung auscultation and CXR

According to our findings, physicians seem to have high confidence in focal chest sounds at auscultation in the assessment of pneumonia both before and after CRP testing, and do not fully trust a negative CXR outcome but prescribe antibiotics anyway. This behaviour was the same both in the intervention group and in the control group. This is interesting in several aspects. As mentioned above, lung auscultation has been shown to be insufficient for the detection of radiologically confirmed pneumonias when used alone [78]. Furthermore, radiographic pneumonia is not always present, not even when the patient presents with LRTI and antibodies against *S. pneumoniae* [127]. Moreover, a study from an emergency department indicated that one third of patients who had no consolidation on CXR had changes consistent with pneumonia on CT scans [128]. This knowledge, and the fact that pneumonia may be lethal, might also influence the physicians in their assessment. However, in clinical praxis, if ordering CXR to exclude or confirm the diagnosis of pneumonia, it would make sense to prescribe antibiotics only in cases with positive findings.

CRP influences the doctor's degree of suspicion of pneumonia

CRP seems to be important in the initial judgement when pneumonia is suspected, in particular when the physician has a lower degree of suspicion, because in one third of cases, the suspicion of pneumonia could be dismissed after CRP testing.

CRP as a piece of the puzzle

The role of CRP testing in the management of respiratory tract infections has been widely discussed, and several studies have evaluated the test as a diagnostic aid with different results. It is not recommended as a single predictor of CAP, but can be helpful in the assessment because it might add information to the clinical examination, and thus act as decision support [70,73,129–131]. In a few cases, the physician had a strong degree of suspicion despite a CRP level below 50 mg/L, and in those cases, CXR was positive (**Paper I**), indicating that other findings have a high impact on the physician's decision making.

The use of diagnostic tests increases

Diagnostic testing has increased in the assessment of pneumonia and acute bronchitis in primary care over time. The increase in microbiological testing, in particular PCR for *M. pneumoniae*, indicate a concern of an origin other than pneumococci. However, the test is used to a low extent and the increase does not seem to have influenced the overall choice of antibiotics. During the same period, antibiotic prescriptions for acute bronchitis have decreased.

Even though prescriptions of phenoxymethylpenicillin increased for pneumonia, the proportion of doxycycline prescriptions remained surprisingly high. The period prevalence of pneumonia peaked in 2011/2012, when there was an outbreak of *C. mycoplasma*, but was otherwise stable over time. Thus, there is no indication that there has been a diagnostic shift. The high proportion of doxycycline prescriptions might possibly reflect the physicians' concern about missing a serious infection caused by bacteria other than *S. pneumoniae* [132]. The fact that the median CRP was lower in those who were prescribed broad-spectrum antibiotics support this theory. Some of the doxycycline prescriptions are probably explained by allergy to penicillin. Since the prevalence of penicillin allergy has been reported to be 5%–10% in the general population [133], most of the doxycycline prescriptions do not seem to be due to allergy.

The decrease in antibiotic prescriptions for acute bronchitis is encouraging, although the prescription rate was still high in 2014 (>40%). This material also includes patients with COPD and smokers, which may explain the choice of doxycycline in some cases. The smoking incidence in Sweden was 14% in 2006 and 10% in 2014 [134]. Another explanation for non-adherence to guidelines could be knowledge gaps among prescribers [135].

Methodological considerations

The major strength of **Papers I–IV** is that they reflect routine clinical work at PHCCs, aiming to improve clinical judgement. Another major strength of **Papers I–III** is their prospective design. In **Papers I–III**, only patients with symptom duration of 24 hours or more were included, which is also a strength because early cases of pneumonia might not be detected on CXR.

The primary reason for exclusion of patients living in nursing homes was the inconvenience when referring fragile elderly individuals for CXR. Moreover, symptoms may be more diffuse in this group [136]. Patients with known COPD were not included because they more often present with acute exacerbation of COPD, for which treatment recommendations differ because bacteria other than *S. pneumoniae* are involved [11].

The intervention in **Paper II** seemed to be well implemented, and the fact that patients in different counties were included is an advantage that may counteract local clinical routines as a confounder.

All the studies in the thesis may have included patients with primary immunodeficiencies or on immunosuppressive treatment, which may have affected the management or choice of antibiotics in a few cases but probably not the overall results. In patients with frequent respiratory tract infections, the prevalence of IgA deficiency (the most common immunodeficiency) has been shown to be 1.5% [137].

Papers I and II included patients from two health care centres in ordinary clinical routine. The most important limitation is that we do not have a perfect gold standard for the diagnosis of pneumonia to rely on, that is, we cannot be sure that some patients may have had pneumonia despite a

negative CXR. However, it has been suggested that symptoms are less severe among patients with radiographically diagnosed pneumonias and who were not clinically diagnosed [138]. Whether or not those pneumonias are self-limiting to a greater extent, and do not need antibiotic treatment, is not known. Another limitation in **Papers I and II** was that, as the physicians participated on a voluntary basis, they did not get extra time to include patients for scientific follow-up, which may have affected the number of patients recruited, and may even have skewed the selection. Furthermore, there was no upper limit of symptom duration, which might have resulted in inclusion of some patients with chronic, rather than acute, symptoms. In **Paper I**, we also lacked information on symptom duration, which is a limitation because the duration has an impact on CRP levels. Moreover, identification of possible study participants was made after clinical examination; hence, in some cases, the physician may have dismissed the diagnosis of pneumonia after CRP testing. This information is lacking

The lack of randomization in **Paper II** is a limitation but would probably not have been suitable. However, cluster randomization could have been a possibility. The proportion of patients referred for CXR in the control group was 26%, which is much higher than the frequency in **Paper IV**, where the rate was 12% in 2014. However, in that paper, the diagnosis was pneumonia and not only suspected pneumonia. The high frequency of CXR could indicate selection bias or that the assessment has changed.

The major limitation in **Paper III** is the lack of a reference standard, which is discussed in more detail in the next section. It might have been better if this study had been part of **Paper I**, where all patients were referred for CXR.

Paper IV evaluated diagnostic testing over time from a large study population. The data were from a whole county, thus minimizing selection bias. Documentation of tests performed is likely to be reliable. Moreover, the register is complete for primary care, and there was no data loss from, for example, private surgeries. We included not only acute bronchitis and pneumonia but also cough, to cover any cases where the physician was not sure of the diagnosis and therefore decided on a symptom diagnosis, but prescribed antibiotics anyway. A limitation is that upper respiratory tract infections (URTIs) were not included. There is a possibility that GPs include URTI as a differential diagnosis in these patients, and when pneumonia is excluded, the diagnosis of URTI is made. However, the period prevalence of acute bronchitis was quite high, which contradicts that explanation.

Strengths and limitations of the project with regard to the primary care clinical context

All studies in this thesis were performed in a clinical context, and patients were included without excluding cases of multi-morbidity. Thus, the studies are pragmatic and reflect everyday work at Swedish PHCCs, which is a strength.

In **Paper I–III**, the inclusion of patients was done in ordinary everyday clinical work at the PHCCs. All physicians (from interns to residents and GPs) at the PHCCs were invited to participate. A strength with this pragmatic approach is that the results can be generalizable to many different settings. On the other hand, a limitation is that the clinical settings may differ between the PHCCs, and it would have been a better idea to recruit from more settings [139].

In **Paper III**, we explored to what extent the physician's degree of suspicion is affected by the CRP result when CAP is suspected in primary care. The main strength is that the study is "close to clinic" and truly reflects how CRP testing contributes to decision making and plays a role as a piece of the puzzle. Its prospective design is also a strength. However, because evaluating CRP testing as a predictor for pneumonia was not the aim, there were no CXR examinations or antibiotic prescription rates as reference standards in this study, which is a limitation. The study was part of a parallel study (**Paper II**) in which there was an intervention to refer some patients for CXR. Therefore, only some patients were referred for CXR and the decision to prescribe antibiotics could be affected by the outcome of CXR. Swedish GPs are comfortable with CRP testing, since it has been available since the 1990's. The generalizability of the results can be affected by the fact that the availability of CRP testing is not same in all countries.

Clinical diagnosis

The finding that the physician's degree of suspicion correlates to CXR findings is interesting. Since the suspicion degree 'sure' had a higher PPV than $\text{CRP} \geq 50 \text{ mg/L}$ and the opposite conditions applied for an NPV, it is likely that physicians should believe in their clinical diagnosis when sure of the diagnosis but when not sure, CRP can be used and if $\text{CRP} < 50 \text{ mg/L}$ pneumonia might be ruled out, provided that the symptom duration has been taken into account.

In the diagnostics of pneumonia, factors other than CRP probably contribute to the decision making, e.g. anamnestic details, clinical examination findings, or the impression of the patient's general health. Moreover, the GP-patient relationship might add information to the situation, because the GP may be familiar with the patient's background and baseline condition [140]. It has been suggested that the most important factor in the assessment of patients is history taking, and that clinical examination and laboratory findings only count for a small part of decision making [141]. It would be of interest to investigate how, and to what extent, other clinical information, as mentioned above, affects the physician's degree of suspicion to better understand the essence of clinical decision making.

CONCLUSIONS AND FURTHER PERSPECTIVES

Conclusions and implications for clinical practice

The findings in this thesis support the current Swedish guidelines that CRP is not necessary in the initial judgement when the diagnosis of pneumonia is clear but could be of value when unsure of the diagnosis.

CXR was used to a fairly large extent at the PHCCs studied. Surprisingly, the physicians did not fully trust CXR findings and often prescribed antibiotics despite a negative CXR. We do not know why that is. Further studies are needed to investigate this phenomenon. When CXR is already used to such an extent, the prescription of antibiotics does not change when CXR is used to an even greater extent. Further, adherence to the current Swedish treatment guidelines is weak as the use of doxycycline is high in the management of pneumonia in primary care.

This thesis has shed light on the diagnostic process of pneumonia in primary care. The primary care physician's degree of suspicion seems to be an important factor in the assessment. When CRP is used, it contributes to the assessment of pneumonia to a high extent and often results in a clinical judgement to dismiss the diagnosis. However, when sure of the diagnosis of pneumonia, CRP testing never results in ruling out the diagnosis, whereas a negative CXR result does not necessarily result in refraining from prescribing antibiotics. Since CXR is not a perfect gold standard and is far from available for everyone, the results from this thesis, where the intervention did not result in reduced antibiotic prescription rates, indicate that CXR is of less value in the primary assessment of pneumonia in primary care. Maybe it is the absence of a diagnostic algorithm and inconsistent guidelines that drive diagnostic testing in the assessment of LRTIs in primary care.

Further perspectives

The reality of primary care is complex. GPs assess a lot of patients, of all ages, with different life situations, and with various diseases, every day. Many of them have multi-morbidity and are thereby prescribed a plethora of medicines. Due to this complexity, it is important to perform primary care research in this context. However, most research is usually not performed within this complex group of patients. Hence, there is a difficulty in generalizing those results into primary care. Thus, in primary health care settings, there is a need for novel and multiple primary care research settings to enable better understanding and assessment of our patients. It is also important to evaluate research results using novel working methods, and algorithms as diagnostic tools, in primary health care settings.

This thesis focused on the diagnostic process of pneumonia and antibiotic prescription. It is also important to evaluate whether the patient can be treated as an outpatient or if there is a need for hospital care. The decision aids that are available often focus on patients in emergency units and are not applicable to primary care. In the pandemic era of Covid-19, this has been even more difficult, because the patient's condition might rapidly deteriorate. Therefore, it is important to evaluate the general condition of the patient and whether there is a safety net. However, in primary care, there is a possibility of follow-ups, either by phone contact or revisits, where the progress of symptoms can be followed.

There seems to be a perceived need for diagnostic tools in the assessment of pneumonia. In the pandemic era of Covid-19, CXR is even less suitable than before in outpatient care of patients with suspected pneumonia. CRP might be helpful to some extent, but a more accurate diagnostic test that could differentiate between bacterial and viral infection in combination with a more suitable examination method for imaging to diagnose pneumonia would improve the diagnostic process. Point-of-care ultrasonography of the lungs might be a possibility for the future, but there are some challenges as discussed earlier; for example, the fact that it is operator dependent. Therefore, it would be of interest if the examination could be combined with artificial intelligence based on artificial neural networks for pattern recognition to develop a decision aid.

The high proportion of doxycycline treatment in pneumonia is surprising. That might be explained by the physician's concern about infections with other bacteria. Maybe experience of repeated treatment failure is behind this behaviour, and thereby it is a justified concern? Or are there knowledge gaps? It would be interesting to examine to what extent treatment failure occurs when phenoxymethylpenicillin is used as first-line treatment of pneumonia in primary care.

In the diagnostic process for pneumonia, factors other than CRP probably contribute to the decision making, e.g. anamnestic details, clinical examination findings, or the impression of the patient's general condition. It would be of interest to investigate how, and to what extent, other clinical information, as mentioned above, affects the physician's degree of suspicion in order to better understand the essence of clinical decision making.

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can be found by those who dares to get lost”*

Tomas Tranströmer

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