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Antibiotic Prescribing in Primary Care

Studying the Management of Infections using Real-World Data

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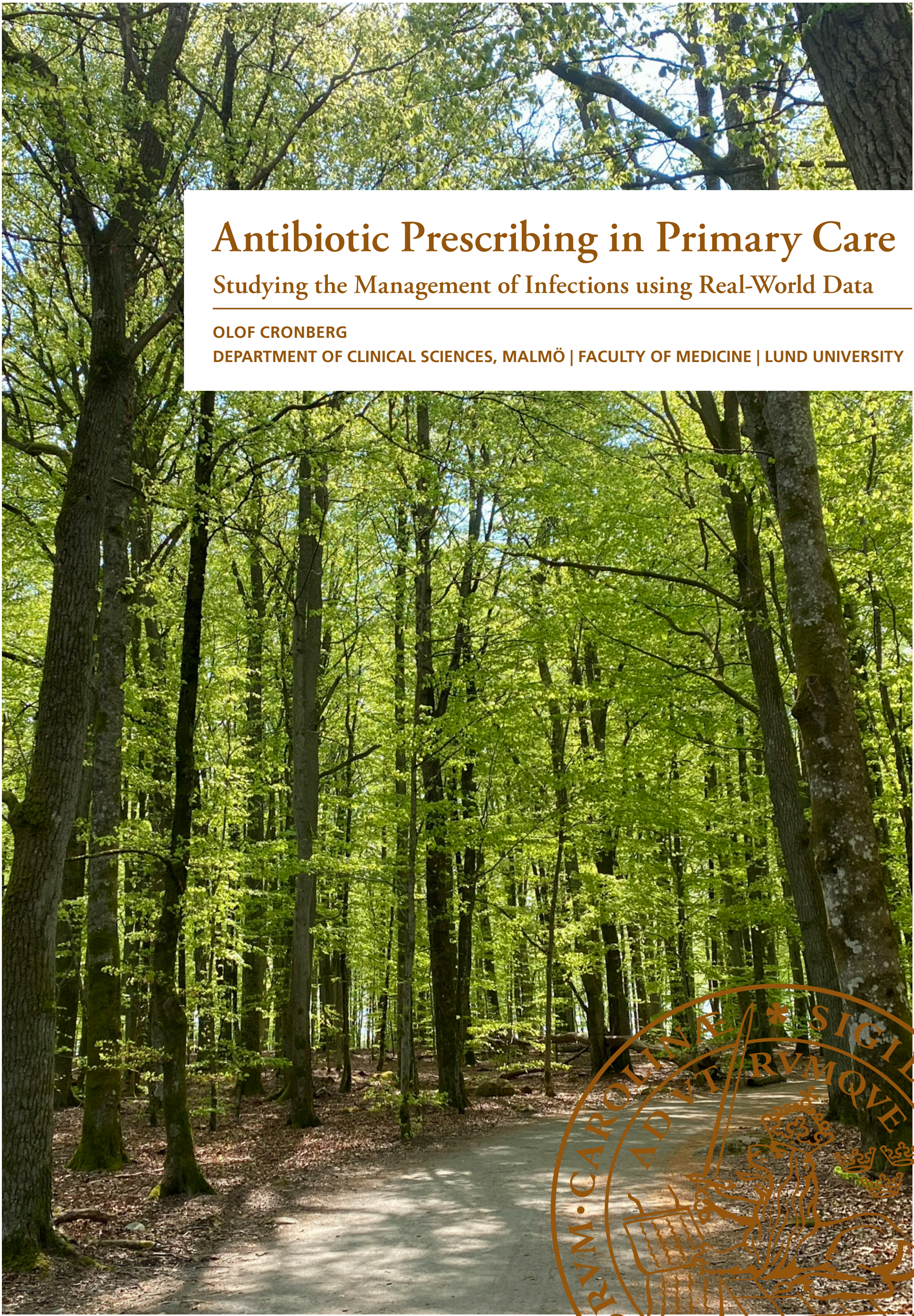

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OLOF CRONBERG graduated as a medical doctor from Lund University in 1989 and has been working as a general practitioner since 1995. Currently, he works at Växjöhälsan Primary Health Care Centre in Växjö, Sweden.

Following the tradition of his father and maternal grandfather, both physicians in Malmö, Sweden, and specialists in Infectious diseases, the topic of this thesis is infections in primary care, with a special focus on the variability of antibiotic prescribing. Primary care plays a crucial role in the fight against antimicrobial resistance, as most infections are treated there. However, there is a large variability in antibiotic prescribing among physicians. Which factors are involved in the process of antibiotic prescribing? Is it possible to reduce the variability and to find an optimal prescribing level?

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Antibiotic Prescribing in Primary Care

Antibiotic Prescribing in Primary Care

Studying the Management of Infections using Real-World Data

Olof Cronberg

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on November 21st at 13.00 in the Agardh Hall, CRC, Department of Clinical Sciences, Malmö, Jan Waldenströms gata 35, SUS, Malmö

Faculty opponent

Professor Guri Rørtveit

Director General, Norwegian Institute of Public Health, Oslo, Norway

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Document name: Doctoral dissertation **Date of issue:** 21 November 2025

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Title and subtitle: Antibiotic Prescribing in Primary Care – Studying the Management of Infections using Real-World Data

Abstract:

There is considerable variation in antibiotic prescribing rates among physicians, primary healthcare centres, and countries. If the variation could be reduced, the antibiotic prescribing could decrease.

Methods. The thesis is based on real-world data from two databases containing infection visits: The Kronoberg Infection Database in Primary Care (infection visits in the Kronoberg region from 2006 to 2014) and the South Sweden Database (infection visits in four regions from 2018 to 2021). The statistical analyses include comparisons between groups using Chi-squared tests, binary logistic regression, and propensity score matching. The possibilities and hurdles of using real-world data are presented.

Results. We found a general decline in antibiotic prescribing in spite of stable infection visits. The decline was more pronounced in children and in respiratory tract infections. No excess antibiotic prescribing during out-of-hours when adjusting for sex, age and diagnoses. No excess prescribing of broad-spectrum antibiotics during out-of-hours (Paper I). The use of point-of-care tests increased for acute bronchitis and pneumonia over a nine-year period. Also, the use of chest x-rays and microbiological tests increased, but remained at a low level (<5 %). Fewer antibiotics were prescribed in acute bronchitis (Paper II). Most physicians reduced their antibiotic prescribing over a nine-year period. Nine out of ten low prescribers remained low prescribers. Interpretation of diagnostic testing explained differences in antibiotic prescribing levels. Seeing a low-prescribing physician did not result in more return visits or secondary antibiotic prescriptions (Paper III). Penicillin V was comparable to amoxicillin in the treatment of pneumonia. We found a general reduction of respiratory tract infections during the COVID-19 pandemic (Paper IV).

Implications. Penicillin V remains the first-line treatment for pneumonia. Physicians can decrease their antibiotic prescribing. Promote not using point-of-care tests without an indication. Interventions focused on out-of-hours centres are not necessary. Further reductions in antibiotic prescribing are possible.

Keywords: antibiotic prescribing, infections, out-of-hours, pneumonia, primary care, variation

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Coverphoto by Olof Cronberg – The road to knowledge passes through Bokhultet

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To Léonie, Stig & Silima

Table of Contents

Abstract

There is considerable variation in antibiotic prescribing rates among physicians, primary healthcare centres, and countries. If the variation could be reduced, the antibiotic prescribing could decrease.

Methods

The thesis is based on real-world data from two databases containing infection visits: The Kronoberg Infection Database in Primary Care (infection visits in the Kronoberg region from 2006 to 2014) and the South Sweden Database (infection visits in four regions from 2018 to 2021). The statistical analyses include comparisons between groups using Chi-squared tests, binary logistic regression, and propensity score matching. The possibilities and hurdles of using real-world data are presented.

Results

We found a general decline in antibiotic prescribing in spite of stable infection visits. The decline was more pronounced in children and in respiratory tract infections. No excess antibiotic prescribing during out-of-hours when adjusting for sex, age and diagnoses. No excess prescribing of broad-spectrum antibiotics during out-of-hours (Paper I).

The use of point-of-care tests increased for acute bronchitis and pneumonia over a nine-year period. Also, the use of chest x-rays and microbiological tests increased, but remained at a low level (<5 %). Fewer antibiotics were prescribed in acute bronchitis (Paper II).

Most physicians reduced their antibiotic prescribing over a nine-year period. Nine out of ten low prescribers remained low prescribers. Interpretation of diagnostic testing explained differences in antibiotic prescribing levels. Seeing a low-prescribing physician did not result in more return visits or secondary antibiotic prescriptions (Paper III).

Penicillin V was comparable to amoxicillin in the treatment of pneumonia. We found a general reduction of respiratory tract infections during the COVID-19 pandemic (Paper IV).

Implications

Penicillin V remains the first-line treatment for pneumonia. Physicians can decrease their antibiotic prescribing. Promote not using point-of-care tests without an indication. Interventions focused on out-of-hours centres are not necessary. Further reductions in antibiotic prescribing are possible.

Populärvetenskaplig sammanfattning

De allra flesta läkarbesöken för infektioner sker i primärvården. En hög och olämplig antibiotikaförskrivning innebär risker inte bara för biverkningar för patienten utan också för ökad antibiotikaresistens. Stora ansträngningar har gjorts för att minska antibiotikaförskrivning. Under covid-19-pandemin såg vi att antalet infektioner och antalet antibiotikaförskrivningar halverades. Hur kan vi fortsätta att ha en låg antibiotikaförskrivning?

Vi vet att det är en stor variation mellan läkare hur stor andel av infektions-patienterna som får antibiotika. I ett material från Region Kronoberg förskrevs vid infektionsbesök antibiotika till mellan 20 % och 80 % av patienterna beroende på läkare. På samma sätt varierade förskrivningen per vårdcentral mellan 28 % och 58 %. Om man skulle kunna minska spridningen, och fler läkare blev lågförskrivare, skulle vi kunna få ner olämplig antibiotikaförskrivning.

För att studera detta närmare skapade vi för artikel I-III en databas baserad på registerdata från verkliga livet kallad Kronobergs infektionsdatabas för primärvården. Denna databas består av uppgifter om 700 000 infektionsbesök i Region Kronoberg 2006-2014 med detaljerade uppgifter om patienten, besöket, vårdgivaren, undersökningarna och antibiotikaförskrivningarna. För artikel IV använde vi en databas för södra Sverige. Denna databas består av uppgifter om vårdkontakter i fyra regioner (Halland, Jönköping, Kronoberg och Skåne) 2018-2021 även här med detaljerade uppgifter som länkats samman. Här studerade vi ett utdrag med 34 000 fall av lunginflammation.

Den statistiska analysen innefattade jämförelser mellan grupper med Chi-2-tester, binär logistisk regression och propensity score matchning. Möjligheterna och svårigheterna att använda data från verkliga livet beskrivs utförligt.

I artikel I beskrev vi infektionsbesök och antibiotikaförskrivning utvecklades under nio år i relation till ålder, kön och diagnos med deskriptiv statistik och linjär regression för tidstrend. Vi fann att det skedde en minskning av antibiotika-förskrivning, trots att antalet infektionsbesök låg stilla. Minskningen skedde främst för barn och vid luftvägsinfektioner. Vi undersökte också antibiotika-användningen jourtid. Det anses att det sker en betydande överförskrivning av antibiotika jourtid, men när vi justerade för ålder, kön och diagnos var överförskrivningen blygsam varför det inte lönar sig att göra interventioner mot just jourverksamheten.

I artikel II var fokus på nedre luftvägsinfektioner (lunginflammation, akut bronkit och hosta) hos vuxna. Vi studerade användning av den patientnära analysen CRP (snabbsänka), lungröntgen och mikrobiologiska test. Vi fann att CRP-test användes allt mer under perioden och oftare vid lunginflammation än vid akut bronkit. Även lungröntgen och mikrobiologiska tester ökade något, men det vara bara 5 % som gjorde respektive undersökning. Under period minskade andel patienter med akut bronkit som fick antibiotika.

I artikel III studerade vi faktorer som påverkade variationen i diagnostiska tester och behandlingar vid luftvägsinfektioner hos olika förskrivargrupper. Baserat på skillnad i förskrivning mellan första och sista treårsperioden delades läkarna upp i tre förskrivargrupper: hög-förskrivargruppen, låg-förskrivargruppen och gruppen som minskar sin förskrivning. Vi fann att de allra flesta läkarna minskade sin förskrivning över nioårsperioden. Vi såg också att nio av tio lågförskrivare förblev lågförskrivare. Vi fann ingen skillnad i karaktäristika mellan grupperna, men däremot fann vi att tolkningen av diagnostiska tester skiljde mellan grupperna. Högförskrivarna var mer benägna att ställa en bakteriell diagnos trots lägre CRP-nivåer och behandlade oftare med antibiotika trots negativt snabbtest för halsflussbakterier. Patienter som träffade en lågförskrivande läkare behövde inte komma oftare på återbesök eller få antibiotika senare.

I artikel IV undersökte vi behandling av lunginflammation i primärvården. Riktlinjerna rekommenderar vanligt penicillin som förstahandsval, men vi vet att många patienter får amoxicillin och doxycyklin. Internationella riktlinjer rekommenderar ofta amoxicillin. Vi undersökte därför risken för terapisvikt (sjukhusinläggning eller död, respektive antibiotikabyte) vid behandling med penicillin och övriga antibiotika. Vi fann att penicillin var jämförbart med amoxicillin avseende sjukhusinläggning eller död, där dock de patienter som fått penicillin primärt något oftare fick byta antibiotika. Doxycyklin hade lägre risk för terapisvikt än penicillin men där misstänker vi att det delvis rörde sig om friskare patienter eftersom CRP-nivån var lägre hos dessa patienter. Eftersom studien löpte över covid-19-pandemin såg vi att antalet lunginflammationer minskade kraftig år 2020 och ännu mer år 2021. I huvudsak förändrades inte antibiotikavalet.

Sammanfattningsvis även om antibiotikaförskrivningen har minskat över tid kvarstår samma variabilitet som tidigare. Vi har funnit att vanligt penicillin även fortsättningsvis kan vara förstahandsläkemedel vid lunginflammation. De flesta läkare har minskat sin antibiotikaförskrivning över tid. Fokus på hur man handlägger infektioner och bara ta patientnära tester där det finns indikation skulle kunna minska förskrivningen ytterligare. Skillnaden mellan kontorstid och jourtid är så liten att interventioner riktade mot jourverksamhet inte är nödvändiga. Med tanke på att variationen kvarstår är det rimligt att tro att ytterligare minskning av onödig antibiotikaförskrivning är möjlig.

List of Papers

Paper I

Cronberg O, Tyrstrup M, Ekblom K, Hedin K. (2020) Diagnosis-linked antibiotic prescribing in Swedish primary care - a comparison between in-hours and out-of-hours. BMC Inf Dis 20, 616 (2020).

https://doi.org/10.1186/s12879-020-05334-7

Paper II

Moberg AB, Cronberg O, Falk M, Hedin K. (2020) 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 May 1;4 (1).

https://doi.org/10.3399/bjgpopen20X101015

Paper III

Cronberg, O., Tyrstrup, M., Ekblom, K., & Hedin, K. (2024). Factors influencing antibiotic prescribing for respiratory tract infections in primary care – a comparison of physicians with different antibiotic prescribing rates. Scandinavian Journal of Primary Health Care, 42 (3), 424–434.

https://doi.org/10.1080/02813432.2024.2332757

Paper IV

Cronberg, O., Tyrstrup, M., Beckman, A., Carlsson, S., Ekblom, K., Moberg, A. & Hedin, K. (2025). Penicillin V as first-line treatment of pneumonia in primary care – a registry-based study. Clinical Microbiology and Infection. Published online. In press.

https://doi.org/10.1016/j.cmi.2025.08.016

Author's contribution to the papers

Paper I

The author, Olof Cronberg, and the supervisor, Katarina Hedin, initiated the study. The author managed and validated the dataset. The author also analysed the data and drafted the manuscript, which all co-authors evaluated. All authors critically revised and approved the final manuscript.

Paper II

Anna Moberg and Katarina Hedin initiated the study. The author, Olof Cronberg, managed and validated the dataset, including interpreting all x-rays results. Anna Moberg also carried out the data analysis and drafted the manuscript, which was evaluated by Olof Cronberg and the other co-authors. All authors critically revised and approved the final manuscript.

This paper has earlier appeared in the thesis by Anna Moberg (Moberg, 2020).

Paper III

The author, Olof Cronberg, and the supervisor, Katarina Hedin, initiated the study. The author managed and validated the dataset. The author also analysed the data and drafted the manuscript, which was evaluated by all co-authors. All authors critically revised and approved the final manuscript.

Paper IV

The author, Olof Cronberg, and the supervisor, Katarina Hedin, initiated the study. Together with Anders Beckman, the author managed and validated the dataset. The author also analysed the data and drafted the manuscript, which was evaluated by all co-authors. All authors critically revised and approved the final manuscript.

Abbreviations

AI	Artificial intelligence
AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical Classification
CRP	C-reactive protein
EMR	Electronic medical records
GAS	Group A Streptococci
IH	In-hours
KIDPC	The Kronoberg Infection Database in Primary Care
LRTI	Lower respiratory tract infection
OOH	Out-of-hours
OOHC	Out-of-hours centre
PCR	Polymerase chain reaction
PHCC	Primary Health Care Centre
PRIS	The Primary Care Record of Infections in Sweden database
RADT	Rapid Antigen Detection test
RTI	Respiratory tract infection
SSD	The South Sweden Database
SSI	Skin and soft tissue infection
STRAMA	The Swedish strategic programme against antibiotic resistance
UTI	Urinary tract infection

Overview of the thesis

Table 1. Overview of the thesis

Paper	Paper I	Paper II	Paper III	Paper IV
Aims	To investigate time trends in antibiotic prescribing by diagnoses, including a comparison between office hours and out-of-hours.	To assess the use of diagnostic tests in lower respiratory tract infections and the change over time.	To investigate trends in diagnostic testing and antibiotic prescribing on the physician level by comparing high, decreasing, and low prescribers.	To investigate the therapeutic failure rate for different antibiotics in pneumonia.
Methods	Retrospective registry-based study. Trends are reported using descriptive statistics and linear regression for time trends.	Retrospective registry-based study. Analysing the use of diagnostic tests in relation to diagnoses and antibiotic prescribing.	Retrospective registry-based study. Comparison of change over time in three prescriber groups using Chi-2-tests.	Retrospective registry-based study. Comparing Penicillin V (PcV) to amoxicillin for the outcome of hospitalisation or death using binary logistic regression.
Results	Stable consultation rates but decreased antibiotic prescribing. After adjusting for diagnoses, the antibiotic prescribing rate is only slightly higher during out-of-hours	The use of CRP tests increased for pneumonia and acute bronchitis. The use of chest x-rays remained low. The antibiotic prescribing for acute bronchitis decreased.	Most physicians reduced their antibiotic prescribing over a nine-year period. Interpretation of diagnostic testing and diagnosing bacterial diagnoses explained differences in antibiotic prescribing levels.	There was no difference between pneumonia cases treated with PcV and amoxicillin regarding the risk of hospitalisation or death. Cases treated with PcV had a higher frequency of antibiotic switch.
Conclusions	No need for intervention at out-of-hours centres to lower antibiotic prescribing.	The increased use of CRP tests could indicate a perceived need for diagnostic tools.	Challenging physicians' behaviour and focusing on the use and interpretation of point-of-care tests is a possible way to improve antibiotic stewardship	Other countries with resistance patterns similar to Sweden's may consider adding PcV to their guidelines.

Introduction

Infection visits are very common, and antibiotics are often prescribed in primary care. We know that a high level of antibiotic prescribing increases the risk of antimicrobial resistance (AMR). Efforts have been made for decades to reduce this prescription with moderate results. Recently, the COVID-19 pandemic has shown that reducing infections and antibiotic treatment is even more possible, which raises the question of how this reduction can be made permanent. To achieve this, it is vital to understand which components are important for antibiotic prescription. In this thesis, I have tried to explore some of these aspects.

Traditionally, it has been said that too many antibiotics are prescribed outside office hours. We therefore wanted to see if that was the case. Few studies have considered that the patient mix is different when comparing out-of-hours with office hours. With diagnosis-linked data and the same population, it is possible to make a more accurate analysis.

Another aspect is what separates high prescribers from low prescribers, and what factors come into play when some physicians decrease their prescribing. We wanted to see what characterises the group of physicians who decrease their prescribing.

We also know that adherence to treatment guidelines is quite poor when it comes to lower respiratory tract infections. However, it is not clear why this is the case. Do physicians not trust regular penicillin, or do they often suspect mycoplasma infections?

Design aspects

My studies are all based on retrospective data from electronic medical records. The advantage of real-world data (RWD) is that it shows how we truly diagnose and treat infections. The results of the studies will open up new research areas that will require prospective or qualitative studies to extend the knowledge frontiers in this domain.

A main strength of the first three studies in the thesis is that the data was diagnosis-linked, which means that it was possible to connect the antibiotic prescriptions with the diagnosis. The data consisted of a complete dataset for a whole region. All primary care centres and all out-of-hours centres were included, and during this period, there were no alternatives for the population (no online physicians and no private physicians). Another advantage was that it was a long period – nine years – and that it was possible to analyse the changes over time.

The dataset for the fourth study of the thesis was also based on diagnosis-linked data and covered 2.3 million inhabitants from four regions over a four-year period.

In this era of artificial intelligence (AI), it is easy to believe in the use of big data, i.e. large databases with a huge amount of data. However, the acronym GIGO ("*Garbage in, garbage out*") still applies to databases. Thus, significant efforts were made to validate and use the databases as appropriately as possible. This is why, in the course of the work, several different levels of potential data errors were found, which I will report in the section on methodological considerations.

In the end, retrospective data always have some basic problems. Firstly, only data available for extraction was possible to use, and the quality depended on how the data was entered. For example, the prescribed antibiotic drug was correct, but the quality of the dosage or indication depended on the ambition of the physician. Secondly, data not entered in a structured way were not available, for example, disease severity and duration, soft data which the physician may take into consideration (the patient looks sick, will be travelling abroad the next day, is allergic to some drug, or the physician is running late and so forth). Thirdly, unknown confounders are always a problem.

Clinical impact

We are happy to see that antibiotic prescribing has decreased in recent decades, but the main reasons for the decrease are still unknown. This means that it is difficult to know which interventions will be effective. This thesis could point to some pieces of the puzzle of optimal antibiotic prescribing.

Background


Kurtzer Entwurff/
Wie man sich/ so woll bey hereinschleichender/ als
auch würcklich schon verhandener
Pest=Zeit
zu verhalten habe/
Auff E. E. Raths der Stadt Rostock
Begehren auffgesetzt/
von
Joann Jacob Döbeln/ der Medicin Doctore,
P.P. Stadt-Physico, und der Medicinischen
Facultät daselbst p. t. Decano.
Gedruckt bey Jacobus Richeln / E.E. Raths Buchd.

Figure 1. A Brief Guide on How to Conduct Oneself Both When the Plague Is Creeping In and When It Is Already Present.
A description of how to avoid the plague, written by Johann Jacob Döbelius, printed in 1680 in Rostock, Germany.

During the last decades, antibiotic prescribing in Sweden has decreased, but there are still variations amongst regions, primary health care centres (PHCCs) and physicians, indicating a need for improvement. Understanding the reasons for the decrease and for the variation could help find new ways of intervention.

Infections in a historical perspective

Throughout time, mankind has suffered from infections. Many children have been lost to infectious diseases, such as pneumonia, diarrhoea, and viral infections. From time to time, there were epidemic diseases such as plague[1], poliomyelitis[2], smallpox[3] and aids[4]. Knowledge of the causes of the diseases and the treatments thereof has often been limited. In the 16th century, it was believed that the position of planets and stars caused pestilence[5, 6].

For centuries, humoral pathology was the prevailing medical theory, which posited that diseases were caused by an imbalance of the body's fluids – specifically, blood, yellow bile, black bile, and phlegm. In the 1660s, Franciscus Sylvius[7] in Leyden founded the iatrochemical school. The idea was that all life and disease were caused by chemical processes and that universal rules of physics and chemistry should explain medicine. In

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[1] My ancestor Carl Dietrich Heitmüller (1655–1718), MD at Copenhagen University, physician in Norrköping, Sweden, wrote an instruction how to avoid the pestilence – "Wälment råd och förordning om the medel eller läkedomar, hwilka gemene man kan sig förskaffa och bruka, när Gud behagar hemsöka land och städer med then allmänna faarsoten, som kallas pestilents feber".

Another ancestor Johann Jacob Döbelius (1640–1684), MD at Leiden University, town physician in Rostock, Germany, and professor in medicine at Rostock University. He chose to study medicine after a severe pulmonary disease. When the plague was affecting Rostock, he wrote "Kurtzer Entwurff wie man sich so woll bey hereinschleichender als auch würcklich schon vorhandener Pest-Zeit zu verhalten habe auff E. E. Raths der Stadt Rostock begehren auffgesetzt" in 1680. See Figure 1.

[2] My ancestor's brother Christoffer Carlander (1759–1838), MD at Uppsala University, physician in Gothenburg and later in Stockholm, Sweden, described in his medical records some cases of polio (Cronberg & Cronberg, 1965).

[3] My great-grandfather Per August Cronberg (1859–1941), physician in Malmö, Sweden, was involved in the vaccination campaign during the last smallpox epidemic in Malmö in 1932.

[4] My father Stig Cronberg (1935–2023), MD at Lund University, physician in Malmö, specialist in infectious diseases, was from 1975 to 1995 the head of the infection department at the General Hospital in Malmö, during the avert of the aids epidemy.

[5] My ancestor's brother Valentin Trutiger, MD at Bologna University in 1554, physician in Wittenberg, linked the astrological calendar to the occurrence of disease. He had noted that Alt & Neu Brandenburg had been hit by epidemics every time Saturn and Mars met in the signs of Capricorn or Cancer. He predicted that the city would be hit by plague in 1564 and 1566 when Saturn and Jupiter met in the sign of Cancer. His prediction was correct, and therefore, astrological predictions of epidemics were introduced into German almanacks. This was written in a book published in 1563, in which he also provided advice on how to treat the plague with herbal remedies.

[6] My ancestor Gervasius Marstaller († 1578) (the brother-in-law of Valentin Trutiger), MD at Padua University in 1552, physician in Wittenberg, published a book in 1549 where he mixed astrology and medicine.

[7] My ancestor the silk merchant Hans von Utenhove (ca 1570-1637) in Hanau, Germany, sponsored the education of his nephew Franciscus Sylvius [original name: Franz de le Boë] (1614-1672), MD at the University of Basel, professor of medicine at Leiden University. He is often falsely cited as the inventor of gin.

a way, medical practice is still inspired by this school of thought. However, for a long time, the humoral pathology remained the prevailing theory, but in the 19th century, it was challenged by empirical studies. In 1828, Pierre Louis (1787-1872) in Paris performed an early empirical study of patients with pneumonia where he compared early venesection (within four days) to late venesection (days 5 to 9). The mortality in the early group was 44% compared to 25% in the late group, suggesting that venesection was dangerous. In 1849, Joseph Dietl (1804-1878) in Vienna could finally prove that venesection should not be performed (Uddenberg, 2015). In the 19th century, the empirical science of medicine as we know it today developed.

Antibiotics

Today, the World Health Organisation (WHO) uses the term antimicrobials, which is a broader term than antibiotics. Antimicrobials are substances that kill or at least inhibit the growth of microorganisms, such as antifungals for fungal infections, antivirals for viral infections, antiparasitics for parasitic infections, and antibiotics for bacterial infections. However, this thesis is focused on antibiotics.

Antimicrobial drugs have been used for centuries to treat infections. Early examples are mercury for syphilis and quinine for malaria. In 1907, the era of modern antibiotics began with Paul Ehrlich's discovery of Salvarsan, a treatment for syphilis. It was followed, in 1928, by Alexander Fleming's accidental discovery of penicillin (Hutchings *et al.*, 2019). During World War II, scientists in Oxford developed penicillin for clinical use. After the war, penicillin became widely available for prescription (Lobanovska & Pilla, 2017).[8]

Since then, numerous classes of antibiotics have emerged. The Golden Age of antibiotic discovery was from the 1940s to the 1960s. During these years, many classes of antibiotics were discovered, such as aminoglycosides, tetracyclines, macrolides, fusidic acid, cephalosporins, and quinolones, to mention a few. However, in the last decades, few new antibiotics have been developed (Hutchings *et al.*, 2019).

[8] My maternal grandfather Hans Hellsten (1901-1984), MD at Lund University, physician in Malmö, specialist in infectious diseases, has told me about the first case of pneumonia that was treated at the General Hospital in Malmö. It was a man with severe pneumonia that the physicians' thought would die. With a few doses of penicillin, he remarkedly survived.

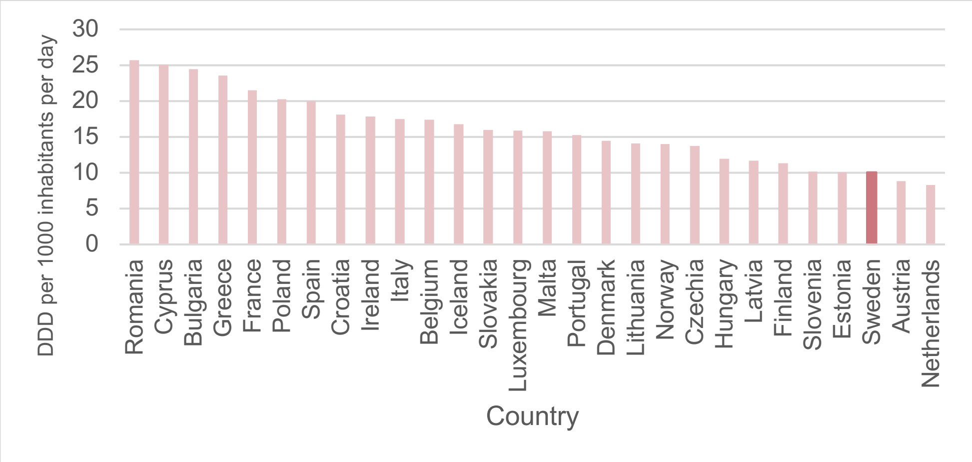


Figure 2. Daily Defined Doses (DDD) of antibiotics per 1000 inhabitants per country in 2021
Source: European Centre for Disease Prevention and Control.

Antimicrobial resistance

Already in the 1920s, bacteria resistant to Salvarsan appeared. Antibiotic resistance to penicillin was discovered in 1942, the same year as penicillin was introduced into clinical use. Today, we know that it is just a matter of time before antibiotic resistance emerges to a new antibiotic. Several groups of multi-resistant bacteria have emerged. Some examples include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase-producing enterobacterales (ESBL).

The WHO has declared increasing AMR a global public health problem and published a global action plan (WHO, 2015). A recent update reports that in 2021, 4.7 million deaths globally were associated with bacterial AMR and projected an increase to 8.2 million in 2050 (GBD Antimicrobial Resistance Collaborators, 2024)

Globally, there is an association between high antibiotic use and high levels of AMR (Abejew *et al.*, 2024). In Europe, there are high levels of antibiotic use and AMR in Southern and Eastern Europe (European Centre for Disease Prevention and Control, 2024). The same pattern is seen in primary care in Europe with high antibiotic use and high levels of AMR reported in Italy and Spain (Sijbom *et al.*, 2023).

The Netherlands and the Scandinavian countries have a low use of antibiotics (Figure 2) and have, to date, maintained a low level of AMR (European Centre for Disease Prevention and Control, 2024). We hope that the AMR will remain at a low level.

Infections in Primary Care

Many infections are identified and treated in primary care (Swedres-Svarm, 2025). There are three main groups of infections in primary care: respiratory tract infections (RTIs), urinary tract infections (UTIs), and skin and soft tissue infections (SSIs). RTIs can be divided into upper respiratory tract infections (URTIs) such as pharyngotonsillitis, acute otitis media, sinusitis, and common cold, and into lower respiratory tract infections (LRTIs), for example, pneumonia and acute bronchitis. Cystitis, pyelonephritis, and prostatitis are typical UTIs. Abscesses, erysipelas, erythema chronicum migrans, and impetigo are typical SSIs. Often, the aetiology could be either bacterial or viral (Cronberg, 1997).

Studies show that many infections are self-healing, and we tend to use fewer antibiotics. For example, the current guidelines for acute media otitis recommend antibiotic treatment only in severe cases (Folkhälsomyndigheten *et al.*, 2025)

Due to good socio-economic standards, we see few severe cases compared to low-income countries and also few complications (IHME Pathogen Core Group, 2024). Due to good vaccination coverage, especially in the children's vaccination program, we see fewer infections today compared to thirty-five years ago when I started to work (Alfven *et al.*, 2024; Johansson Kostenniemi *et al.*, 2018; Sigurdsson *et al.*, 2015; Vesikari *et al.*, 2016). However, even if complications are rare, we need to treat bacterial infections with antibiotics to avoid relapses and hospitalisations, and in the long run, avoid septicaemia and death.

Primary Care in Sweden

Primary care in Sweden is based on PHCCs with between 2000 and 20,000 listed patients. Typically, at a PHCC, the staff includes physicians (general practitioners/specialists in Family medicine, and junior physicians), nurses, nurse assistants, physiotherapists, behavioural therapists, and administrative staff. A physician is responsible for anywhere between 1000 and 3000 patients. Nurses could have special training in, for example, child health care, diabetes care, asthma/chronic obstructive pulmonary disease care, or dementia care. Home visits are possible for elderly, fragile patients. It is common for the PHCC to be responsible for one or more elderly homes. Regular office hours, in-hours (IH), are between 8.00 and 17.00, but longer hours are possible.

The PHCCs are publicly funded by the region. The reimbursement system used to be budget-based, but in 2009, it transitioned to a capitation-based system, inviting private companies to operate PHCCs. Today, a third of the PHCCs are privately operated, but they are still publicly financed.

Apart from the PHCCs, there are regional phone services of nurses giving health care advice and guiding patients to the correct care level. Since 2017, there have been companies providing access to online physicians (Ekman *et al.*, 2019). These companies are often privately operated and get paid per online consultation by the regions, which, in turn, in most cases charge the PHCCs for the cost.

At the PHCCs, diagnostic tools like C-reactive protein (CRP), Rapid Antigen Detection Test (RADT) for streptococci, and urine tests are generally available. Other laboratory tests could be sent to the closest laboratory with an answer within 24 hours. There are possibilities to refer patients to the nearest hospital for an acute chest x-ray. Point-of-care ultrasound is not available.

A patient with an infection typically calls the PHCC, where a triage nurse gives advice or books an appointment. At the beginning of the period, the appointments were always with a physician, but nowadays the appointments could also be with a nurse.

During the COVID-19 pandemic, special infection tracks were established, where patients with infections were examined in a separate consultation room within the PHCC to limit the spread of the disease. Some PHCCs still have a designated track for infectious patients.

Typically, antibiotic prescriptions are transmitted from the electronic medical record (EMR) system to a national prescription database, allowing patients to collect the prescription immediately at any pharmacy. Patients could have dose-dispensed medications, which is an option for older patients to receive their medication every other week in rolls, with pre-packaged pouches of medication for each dose administration time. In these cases, prescriptions are written in a separate online system.

Outside office hours, there are typically common out-of-hours (OOH) services for several PHCCs. The extent of the services could vary by region. In some regions, the PHCC could choose how to provide this service. During OOH, access to home visits is very limited.

There are some differences between the PHCCs in the regions included in paper IV. Each region has its own set of rules for primary care. The principles, as well as the level of reimbursement, could differ. The way the PHCCs are allowed to provide OOH service could also be different. The regions have different EMR systems. In some regions, the primary and secondary care use the same EMR, and in other regions, they use different EMRs.

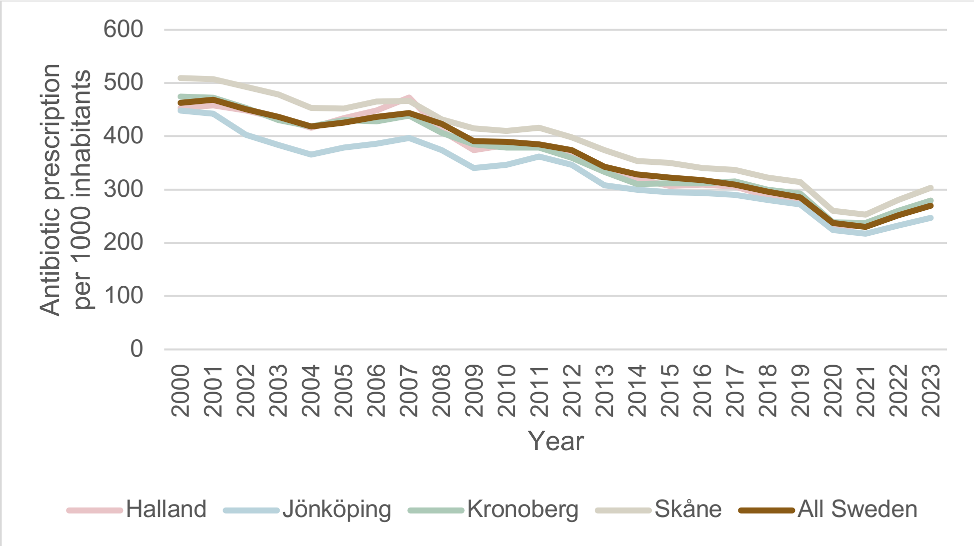


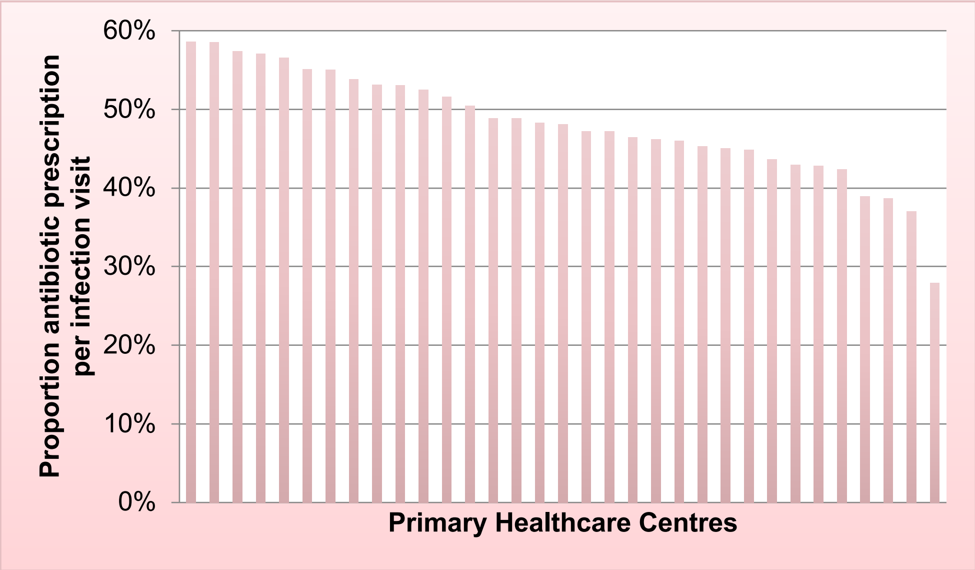
Figure 3. Antibiotic prescriptions in outpatient care per region per year in Sweden 2000-2023. ATC code J01 excluding metenamin. Source: Official statistics from E-hälsomyndigheten.

Antibiotic prescribing

Antibiotic prescribing is the process of identifying an infection and deciding to treat it with antibiotics, and then prescribing antibiotics. Many efforts have been made to decrease antibiotic prescribing in many countries. Multifaceted interventions have been found to be more effective than single interventions (Llor & Bjerrum, 2014)

Since the millennium, antibiotic prescribing in Sweden has decreased by 42% from 463 prescriptions per 1000 inhabitants in 2000 to 270 prescriptions in 2023 (Figure 3). From a European perspective, Sweden is a low-prescribing country (Figure 2).

Although we use antibiotics in many situations with suspected bacterial infections in primary care, for some infections, no studies have been performed showing the effect of antibiotics in treating the infections and avoiding complications. For example, studies of antibiotic treatment of pneumonia in primary care with oral penicillin have not been made. Is the rate of therapy failure of narrow-spectrum penicillin comparable to broad-spectrum antibiotics?



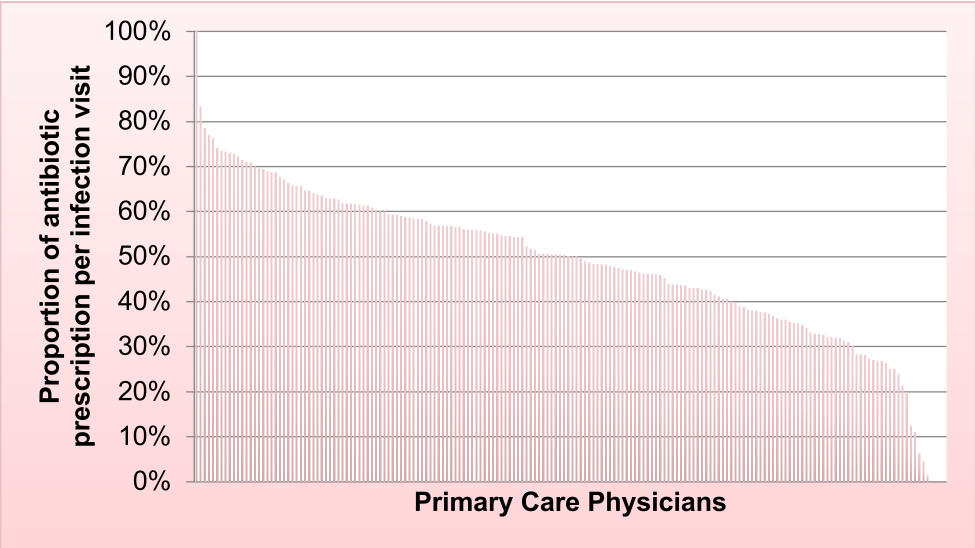


Figure 4. Variation in antibiotic prescribing per primary health care centre and primary care physician, respectively, in the Kronoberg region 2010-2012
Proportion of antibiotic prescriptions per infection visits per primary health care centre and per primary care physician, respectively. Infection visit was defined as a visit with at least one of the following ICD-10 codes: B34, H65-H66, J01-J05, J09.9, J11, J18, J22, J36, J42, J44.1, L01-L05, L08, & R05. Source: Region Kronoberg.

Variability

Studies on antibiotic prescribing in primary care, regardless of indication, reveal large variations between physicians from different countries (Bjerrum *et al.*, 2004; Cars *et al.*, 2001; Tyrstrup *et al.*, 2017). There is also a variation in antibiotic prescribing between regions in Sweden (Hellman *et al.*, 2010) and a variation between PHCCs (McGavock, 1988; Tyrstrup *et al.*, 2016). There are also variations between individual physicians (Nord *et al.*, 2013).

Aggregated data for the Kronoberg region from 2010 to 2012 showed that the antibiotic prescription rate for PHCCs varied between 28% and 58% of infection visits. For individual physicians, the range of antibiotic prescription rate excluding outliers varies between 20% and 80% of infection visits (Figure 4).

It has been claimed that more antibiotics are prescribed during OOH (Edelstein *et al.*, 2017; Hayward *et al.*, 2016). Could over-prescribing during OOH explain some of the variations?

Causes of variability

Different factors can explain the causes of variation. Four main areas could explain variations: (1) random differences, (2) different case mixes and assignments, (3) registration differences, and (4) quality differences (Figure 5).

The first area, random differences, will always be there. However, it is rather difficult to create variation, so in a large dataset, such as in these studies, it would be small. The second area, different case mixes, could explain variability among PHCCs. This difference is normal and perhaps too often used to legitimise differences. The third area, registration differences, could cause variability in data that does not reflect an actual variation. For example, if a PHCC only writes point-of-care test results on paper and not on the computer, it could be hard to spot.

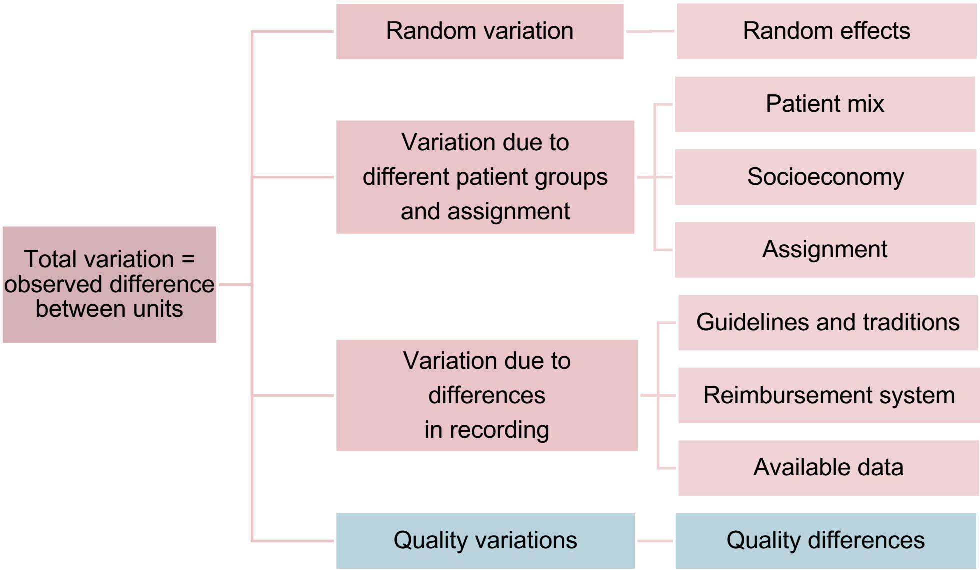


Figure 5. Factors explaining variation.
Source: Adapted from primarvardskvalitet.se.

The fourth area, quality differences, causes unwanted variability. We want to decrease this type of variability. Finding quality differences and trying to reduce them has been an important task for the Swedish strategic programme against antibiotic resistance (STRAMA) (Molstad *et al.*, 2008; Molstad *et al.*, 2017; STRAMA, 2025.) for decades; however, the variability remains large.

Difficult to change?

As mentioned earlier, we have observed a decline in antibiotic prescribing over the past three decades. It is unclear whether this change is due to all prescribers prescribing slightly fewer antibiotics or whether it is due to some prescribers changing their prescribing to a greater extent than others. A small study from 1995 shows that high antibiotic prescribers tend to remain high prescribers, and vice versa, despite targeted interventions (Cars & Hakansson, 1995). Is this study still valid? It is not known if some prescribers are more prone to change the management of infections, and if so, what characterises these prescribers.

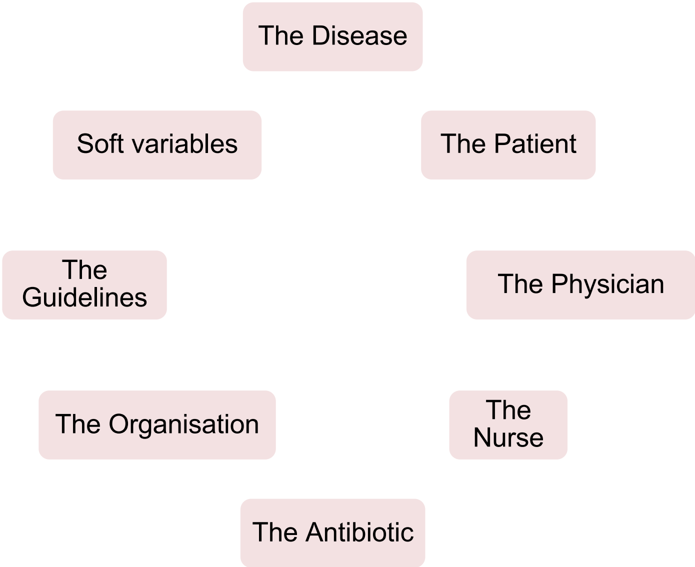


Figure 6. (F)Actors at the scene

(F)Actors

We tend to focus on physicians when discussing antibiotic prescribing and overprescribing, but there are several other factors or actors at the scene that could affect the variability due to quality differences. Additionally, several of the (f)actors interact with one another (Figure 6).

The disease

For some infectious diseases, antibiotics are essential and lifesaving. For other infections, antibiotics are of little use and, in some cases, even harmful. The disease pattern changes over time when epidemics come and go.

The patient

The patient's health status is an obvious variable in the puzzle. Children like the elderly are more prone to severe diseases. However, the patient's earlier experiences are also important. Physicians often claim that patients demand antibiotics, but this is probably based on the physicians' own thoughts (Llor *et al.*, 2013).

The physician

Since the physician evaluates the patient's symptoms and, if needed, prescribes antibiotics, the physician's role is essential. I have already demonstrated that there is a significant unexplained variability between the physicians.

The nurse

Since the patient typically contacts a triage nurse to have an appointment, the nurse's role must not be overlooked. Based on the patient's description, the nurse assesses whether the patient requires a consultation at all and whether the patient needs to see a physician on the same day or can wait.

Traditionally, patients with infectious symptoms have been seen by physicians in primary care. Due to a lack of physicians, some PHCCs have nurse-led infection care, where only cases with more severe symptoms are seen by physicians and may be prescribed antibiotics. The nurses are not allowed to prescribe antibiotics.

The antibiotic

There is a general recommendation to use narrow-spectrum antibiotics to avoid the promotion of AMR. Typically, we should use penicillin for pharyngotonsillitis and pneumonia, pivmecillinam or nitrofurantoin for cystitis, and flucloxacillin for abscesses. We should avoid broad-spectrum antibiotics, such as cephalosporines, tetracyclines, macrolides, and quinolones.

The organisation

Several organisational structures could affect antibiotic prescribing. The current reimbursement system, where the PHCC get capitation for listed patients, could stimulate overprescribing to be "kind" to the patient. Easy access, such as online consultations or walk-in clinics, may increase the risk of promoting prescription. There is a concern that nurse-led infection visits may lead to increased antibiotic prescribing. With the COVID-19 pandemic, the PHCCs had to find a separate examination room for infectious patients, which limited the number of patients they could treat. When the polymerase chain reaction (PCR) test for COVID-19 was the only available test, the patient had to wait 2-3 days for the result before seeing a physician.


GÄLLER FRÅN 2025-03-19

Behandlingsrekommendationer
för vanliga infektioner i öppenvård

Tecken på allvarlig infektion hos vuxna och barn
Akut mediaotit
Rinosinuit
Faryngotonsillit
Akut bronkit och pneumoni
Akut exacerbation av KOL
Urinvägsinfektioner
Hud- och mjukdelsinfektioner
Sexuellt överförbara bakteriella infektioner

Folkhälsomyndigheten
LÄKEMEDELSVERKET
Strama

Figure 7. The Rainbow booklet. Guidelines of common infections in outpatient care.
The booklet is published by The Public Health Agency of Sweden, Swedish Medical Products Agency and STRAMA - the Swedish strategic programme against antibiotic resistance.

The guidelines

At the international level, guidelines for Lower Respiratory Tract Infections (LRTIs) were published in 2011 (Woodhead *et al.*, 2011). For infectious diseases in primary care, there are specific guidelines by the Public Health Agency of Sweden, the Swedish Medical Product Agency, and STRAMA – the Rainbow Booklet (Folkhälsomyndigheten *et al.*, 2025). See Figure 7.

Soft variables - the recognition of special circumstances

One (f)actor that could explain some of the variability is the physician's sensitivity to soft variables – special circumstances. Sometimes, the patient says that he is going to travel abroad, that his partner is sick, that he was severely ill last time or that he has some other problem. Sometimes, the physician wants to be cautious, especially since it is Friday afternoon, he is running late, or he thinks the patient desires antibiotics. How often do the physicians step outside the guidelines due to soft variables?

Summary of (f)actors

Some of these (f)actors are easier to study than others. In this thesis, I will present studies concerning the diseases, the patients, the physicians, the antibiotics, the organisations and how the result may affect the guidelines. The impact of the nurses and soft variables is difficult to study in registry-based data.

Real-world data

Real-world data (RWD) in medicine is built on linked data relating to a patient's health status and/or the delivery of healthcare that is routinely collected from various sources. These sources can include EMRs, registers of prescribed drugs, cause of death and sick leave. The patient population is more heterogeneous in real-world settings compared to the populations in clinical randomised trials. The idea is that using RWD will lead to real-world evidence (RWE) – evidence-based medicine for a broader population than those participating in randomised clinical trials. (Hiramatsu *et al.*, 2021; Sherman *et al.*, 2016)

RWD has the advantage of demonstrating how we manage our patients in real-world settings. When physicians and patients participate in studies, they often adapt to what is expected.

The disadvantage is that typically only data recorded in a structured format is available. We don't know which data were not recorded at all. Also, limited access to RWD is a challenge. There is also a lack of universally accepted methodological approaches.

Which of the above-mentioned (f)actors can be analysed with RWD? In what way? Can RWD be used to understand variability?

Aims

Overall aim

To investigate factors influencing variability in antibiotic prescribing in primary care and identify the implications of antibiotic choice in the clinical management of infections, aiming for more optimal antibiotic treatment of our patients.

Specific objectives

1. To investigate time trends in antibiotic prescribing by diagnoses, including a comparison between office hours and out-of-hours.
2. To assess the use of diagnostic tests in lower respiratory tract infections and the change over time.
3. To investigate trends in diagnostic testing and antibiotic prescribing on the physician level by comparing high, decreasing, and low prescribers.
4. To investigate the therapeutic failure rate for different antibiotics in pneumonia.

See Table 2 for an overview of the studies.

Table 2. Overview of the studies.

Paper	I	II	III	IV
Design	Retrospective registry-based studies			
Study population	702,048 physician visits for **infections** with 389,263 antibiotic prescriptions including focus on out-or-hours services.	54,229 cases of **lower respiratory tract infections** in patients 18-79 years	166 physicians active in primary care during the whole study period treating **respiratory tract infections**	34,306 cases of **pneumonia** in children >5 years and adults treated in primary care
Period	2006-2014	2006-2014	2006-2014	2018-2021
Data analyses	Comparison between groups with the χ^2 -test. Trends analysed with linear regression for time trends.	Comparison between groups with the χ^2 -test. To analyse change over time, a binary logistic regression model was used. To adjust for confounders, a multiple regression model was used.	Comparison of change over time in three prescriber groups using χ^2 -tests with Bonferroni correction for multiple comparisons.	A binary logistic regression model was used to compare penicillin V to amoxicillin for the outcome of hospitalisation or mortality adjusting for confounders. Propensity score matching was used for the main comparison.

Material and Methods

Introduction

This thesis comprises four papers based on RWD, which are retrospective observational studies. The advantage is that we can evaluate how infections are diagnosed and managed in reality. The disadvantage is that it is impossible to measure many confounders. Also, retrospective datasets can give a false sense of accuracy, as will be commented on later in the Discussion section.

The first three papers are based on the Kronoberg Infection Database in Primary Care, a database of infection visits spanning nine years in the Kronoberg region, Sweden, with a population of 189,000 inhabitants. They are presented together in this section of the thesis. The fourth paper is based on the South Sweden Database, a database of visits from four years in four regions of South Sweden, with a population of 2.3 million. This database will be presented separately.

Kronoberg Infection Database in Primary Care

The first three studies are retrospective analyses using the Kronoberg Infection Database in Primary Care (KIDPC) of all visits with infection diagnoses and all antibiotic prescriptions with/without visits, over a nine-year period (2006-2014) to examine time trends in diagnoses, investigations, prescriptions, and physicians.

The database

The data during nine years (2006-2014) in the KIDPC were extracted from the EMR used in the Kronoberg region (Cambio Cosmic software, Cambio Healthcare Systems AB, Linköping, Sweden) at one instance in 2015 using BusinessObjects (SAP AG, Walldorf, Germany). Kronoberg was the last region to adopt EMR, but since 2004, a common EMR system has been in place for both primary and secondary care. The period was chosen because 2006 was the first year with complete EMR. This data contains detailed information about the patients (age, sex, anonymous ID), the visits

(PHCC, geography, IH or OOH), the care providers (physicians, nurses), the investigations (diagnostic tests, x-rays, cultures), and the prescriptions (drugs, dosages, durations). The data were linked together using the anonymous patient ID and visit date. For all physician visits, at least one diagnosis was registered according to the simplified Swedish primary care edition (KSH-97) of the International Statistical Classification of Diseases and Related Health Problems – Tenth Revision (ICD-10) (Socialstyrelsen, 1997). The database consists of infection visits[9]. No diagnoses were recorded for phone or mail consultations, and in these cases, the prescriptions could not be linked to a diagnosis. Antibiotic prescriptions from the EMR were linked to diagnoses within a week after a visit to include antibiotics prescribed because of a bacterial culture. Antibiotic treatment without a diagnosis of an infection could also result from consultation with a care provider other than a physician or from a non-infection diagnosis at a visit. Information on whether the patients collected the medication at the pharmacies was not available. Antibiotics prescribed to patients with dose-dispensed medication were missing.

Definitions

Diagnosis groups: The infection diagnoses were validated and grouped into four main groups and several subgroups according to recommendations by the Public Health Agency of Sweden (*Folkhälsomyndigheten*) (Folkhälsomyndigheten, 2016). The main groups are Respiratory Tract Infections (RTIs), Urinary Tract Infections (UTIs), Skin and Soft tissue Infections (SSIs), and Other Infections. The RTI group includes ear infections, and the UTI group includes urogenital infections. The Other Infection group includes eye infections, gastrointestinal infections, and rare infections.

Antibiotic prescriptions were identified according to Anatomical Therapeutic Chemical Classification (ATC) code group J01, which includes all oral and parenteral antibiotics, excluding those in ointments or eye drops.

Description of the study population

In 2014, the Kronoberg region in southern Sweden had 189,128 inhabitants, which was equal to 2% of the Swedish population (Statistics Sweden). In total, there were approximately 1300 physician visits for any cause and 1300 other visits (nurses, physiotherapists, behavioural therapists) per 1000 inhabitants. Annually, there were on

[9] The following ICD-10 codes were used: A00-B99, G01-G05, G61, G93.3, H00-H01, H04.3, H10, H60, H65-H66, H70,H72, I30-I31, I33.0, I38, 140, J01-J06, J09-J18, J20-J22, J31-J32, J34.0, J36-J37, J40-J44, J47, K25-K26,K57, K61, K81, L00-L05, L08, L30.3, L60.0, L70-L73, L89, L97-L98, M71.0, N10, N12, N30, N34, N39, N41, N45, N48.1, N70-N73, N75-N76, O86, O91, P38, P39.1, R05, R36, R56, & T15. Details are available in the supplementary data of paper I.

average 86,000 visits for infections and 43,000 antibiotic prescriptions reported in the database, equivalent to 460 visits and 230 antibiotic prescriptions per 1000 inhabitants.

There were 28-35 primary healthcare centres (PHCCs), with 1–8 family physicians working at each. There were approximately 100 family physician positions and 50 junior physician positions. At the study start, all PHCCs were publicly run, but since March 2009, a third of the PHCCs have been privately operated, while still publicly financed.

In the region, there were two OOH centres (OOHCs), and the PHCCs staffed the OOHCs with physicians. Patients were supposed to call a nurse triage first, but could also walk in. The visit fees were the same as for IH visits. Home visits were rare, and usually only performed for urgent cases at elderly care homes. At the time of the study, no telehealth service was available.

Datasets

In Paper I, all physician visits with an infection diagnosis and all antibiotic prescriptions were included, consisting of 702,048 physician visits and 389,263 prescriptions over nine years. For each visit, data on the patient's age and sex, infection diagnoses, antibiotic treatments, and PHCC were included. More than one infection diagnosis was recorded in 3% of the visits. In these cases, the primary diagnosis was selected based on the severity and the likelihood of an antibiotic prescription.

In Paper II, adult patients aged 18–79 years with a lower respiratory tract infection (LRTI) — pneumonia (J18.-P), acute bronchitis (J22.-P), and the symptom diagnosis 'cough' (R05.-) — were eligible for analyses. Contacts occurring within 6 weeks for the same patient and diagnosis were considered a single contact.

In Paper III, data on respiratory tract infections (RTI) visits with information about the patient (age, sex), the physician (age, sex, training level), the PHCC, the diagnostic test (CRP test and RADT for Group A Streptococci (GAS)), and the antibiotic treatment.

The data were divided into three 3-year periods. All 166 physicians who had diagnosed at least one RTI during each of the three periods were identified. The remaining 847 physicians who had not been active during all three periods were excluded. These were locums, interns who did not continue in family medicine, and physicians who moved or retired.

The antibiotic prescribing rate was defined as the number of antibiotic prescriptions at RTI visits divided by the number of RTI visits. The antibiotic prescribing rates for RTIs per 3-year period were calculated for each physician and were adjusted for the patients' sex and age group.

Table 3 Cross-table of adjusted antibiotic prescribing rates in the Kronoberg region per primary care physician comparing the first period 2006-2008 with the third period 2012-2014.
The upper level is an adjusted antibiotic prescribing rate of more than 48%, the medium level is between 40% and 48%, and the lower level is below 40%. The red field represents high prescribers (the High Prescribing Group), the yellow field represents prescribers who have reduced their antibiotic prescription rate (the Decreasing Prescribing Group), and the green field represents low prescribers (the Low Prescribing Group). Source: Paper III.

		Third period			
		Upper	**Medium**	**Lower**	**Total**
First period,	**Upper**	12 (7.2%)	19 (11%)	25 (15%)	56 (34%)
n (% of all)	**Medium**	1 (0.6%)	9 (5.4%)	43 (26%)	53 (32%)
	Lower	1 (0.6%)	4 (2.4%)	52 (31%)	57 (34%)
	Total	14 (8.4%)	32 (19%)	120 (72%)	166 (100%)

The physicians were divided into prescriber groups in three steps. Firstly, they were classified into three equal levels based on their antibiotic prescribing rate during the first period, 2006-2008. Low-level prescribers were defined as those with an antibiotic prescribing rate below 40%, medium-level prescribers as those with a rate between 40% and 48%, and high-level prescribers as those with a rate above 48%. Secondly, during the third period, 2012-2014, the physicians were again divided into three levels using the same cut-offs.

Finally, in the third step, three prescriber groups were identified: The High Prescribing Group (consisting of high- or medium-level prescribers during both the first and the third period), the Decreasing Prescribing Group (consisting of high- or medium-level prescribers during the first period who transitioned to low-level prescribers during the third period), the Low Prescribing Group (consisting of low-level prescribers during both the first and the third period). Five physicians who were low-level prescribers during the first period and medium- or high-level prescribers during the third period were excluded from further analyses, as they did not fit into the predefined prescriber groups (Table 3).

The remaining 161 physicians were included and had 263,000 RTI visits, corresponding to 2/3 of all RTI visits during the period 2006-2014. In total, they had prescribed 108,000 antibiotic prescriptions at RTI visits, accounting for two-thirds of all RTI antibiotic prescriptions during the period (see also Figure 18).

South Sweden Database

The database

Paper IV is a retrospective cohort study based on the South Sweden Database (SSD), which consists of RWD data from EMRs in four regions (Halland, Jönköping, Kronoberg, and Skåne) in southern Sweden, representing a population of 2.3 million. The EMR data are stored in databases in each region, and in this study, data from 2018 to 2021 were extracted from these databases.

At all visits, the physician was obliged to record at least one diagnosis code using ICD-10 or KSH97-P (Socialstyrelsen, 1997; WHO, 2019). The following codes were used: pneumonia (J13-J18), chronic pulmonary disease excluding asthma (J40-J44, J47), and LRTI including COVID-19 and sepsis (J09-J18, J20–J22, J85–J86, J90–J91, and U07; A40–A41 and R65). We retrieved information about deaths from Sweden's National Cause of Death Register.

Also, we collected information on dispensed prescriptions from Sweden's National Prescribed Drug Register, which also contains information on dose-dispensed medication. We included all antibiotics with the three-level ATC code of J01 except nitrofurantoin, pivmecillinam, trimethoprim, and methenamine hippurate, which are only used for UTIs.

We included all pneumonia visits in outpatient care at PHCC and hospitals, and retrieved data on consultations, hospitalisations, deaths, lab results, and antibiotic prescriptions. Due to separate guidelines, we excluded patients aged below five years and patients with chronic pulmonary diseases. Patients on dose-dispensed medication during the current year were excluded, since antibiotic prescriptions could be recorded in several ways and were difficult to retrieve. Finally, this study excluded visits where patients were hospitalised or died on day 0, or did not receive an antibiotic prescription on day 0.

The study period spanned from February 12, 2018, to December 3, 2021, to account for run-in and follow-up periods. The pre-pandemic period was defined as 2018-2019, and the pandemic period as 2020-2021.

Definitions

A case was defined as a pneumonia visit in primary care with no prior LRTI infection or antibiotic treatment during the preceding 42 days.

The primary outcome was hospitalisation for LRTI or all-cause mortality on days 1-28. The secondary outcome was an antibiotic switch, defined as a new antibiotic prescribed on days 1-28 that differed from the initial one on day 0. The exposure variable was defined as the dispensed antibiotic prescription on day 0.

We identified the following available potential confounders: sex, age group, care level, day of the week, pandemic period, comorbidity, and CRP level. Comorbidity was defined as any presence during the study years of diagnoses used in the Charlson Comorbidity Index (CCI) adapted for Sweden [14], with correction for missing diabetes codes in Ludvigsson's algorithm (the missing codes ICD-10 codes E10.8, E10.9, E11.8, and E11.9 are added to the CCI group "Diabetes without complications").

Statistical analyses

For all the studies, we analysed data using SPSS Version 23 or later (IBM Corp, Armonk, NY, USA). The MatchIt package (version 4.5.5) in the statistical software R (version 4.3.2) was used for the propensity score matching. We calculated means (standard deviation, SD), proportions and medians for descriptive data and used Pearson's χ^2 test to compare groups. In skewed data, we used the Mann-Whitney U test. We presented continuous variables with non-normal distribution as medians (interquartile range, IQR), and the Median test was used to compare medians across groups. For annual trends, linear regression was used. P values <0.05 were considered significant.

In Paper I, the data are presented as annual data and mean annual change for infections and antibiotics per 1000 inhabitants, divided per main infection group and per IH and OOH. A cohort comparison between IH and OOH calculated the relative risk of receiving antibiotics during OOH.

In Paper II, we used a binary logistic model to analyse change over time, using the first year as a reference. We used a multiple logistic model to adjust for confounders.

In Paper III, an RTI visit was defined as an index visit if there was no RTI visit in the previous 30 days. A return visit was defined as an RTI visit within 1-30 days of an earlier RTI visit. Antibiotics at return visits were defined if antibiotics were prescribed at a return visit within 30 days of an index visit. These measures were linked to the physician of the index visit. The use and result of point-of-care tests (CRP and RADT) and diagnoses at index visits were also measured. These measures are reported in two ways: 1) numbers per index visits per prescriber group (group level), and 2) numbers per physician per prescriber group (physician level). In the latter case, the data were divided into quartiles.

We analysed the following characteristics of the physicians: sex, birthyear, training level (specialist in family medicine during 0%, 1%-49%, 50%-99% or 100% of the infection visits), continuity (number of PHCC at which each physician has worked where lower number equals to higher continuity), OOH rate (OOH visits per total number of visits per physician), and activity level (total number of RTI visits). At the group level, we used Pearson's χ^2 test to compare groups and Cramer's V to measure the effect size. At the physician level, we divided the data into quartiles, and the prescriber groups were compared using Pearson's χ^2 test. If the comparisons among the three prescriber groups were statistically significant, pairwise comparisons were conducted using the Bonferroni correction (multiplying p-values by three) to account for multiple analyses. To compare the High Prescribing Group with the Decreasing Prescribing Group, a multiple logistic regression analysis with a complete model was performed, using background factors (physicians' sex and birth year) and selected variables significant in univariate logistic regression as independent variables.

In Paper IV, we used binary logistic regression with the enter method to assess the association between the primary outcome, hospitalisation for LRTI or all-cause mortality, and the secondary outcome, antibiotic switch, and the independent variables (age, sex, prescribed antibiotic, CRP level, day of the week, pandemic period, care level, and comorbidity). We presented the results as both unadjusted and adjusted odds ratios, along with corresponding 95% confidence intervals (CI). Subgroup analyses were performed for cases with different CRP levels at day 0, as elevated CRP may indicate more severe pneumonia. Several sensitivity analyses were conducted: children 5-19 years, adults, pre-pandemic and pandemic periods, tobacco use, obesity, and data from Region Skåne and the other regions. We omitted cases with missing data, except for missing CRP results, from the analyses. The instances with missing CRP results were included in all analyses except for the subgroup analyses of cases with different CRP levels. A separate analysis was made for the outcome of all-cause mortality.

Also in paper IV, propensity score matching was performed to evaluate the primary comparison between penicillin V and amoxicillin. The propensity score was obtained from a logistic regression model with antibiotic treatment as the outcome variable. The same covariates used in the primary regression analyses were included as explanatory variables in the propensity score model. Nearest-neighbour matching with a ratio 1:1, with a calliper <0.1 and without replacement, was applied; the outcomes were subsequently assessed using logistic regression.

Method Summary

To summarise, the thesis is based on two databases – in Papers I-III, the KIDPC database was used with data from the Kronoberg region 2006-2014, with data on prescribed drugs but lacking information on dose-dispensed medication, and in Paper IV, the SSD database was used with data from four regions in South Sweden from 2018-2021 with data on collected prescriptions and information on dose-dispensed medication. In Paper I, we analysed all infections for all ages, in Paper II, we analysed LRTI for patients 18-79 years, in Paper III, we analysed RTI for all ages, and in Paper IV, we analysed pneumonia for patients aged 5-100 years without patients with chronic obstructive pulmonary disease or on dose-dispensed medication.

Use of AI tools

"This thesis has been partially produced with the help of the generative AI models Copilot, Grammarly, ChatGPT, and Wayless. I have edited the generated text and take full responsibility for the content." (ChatGPT has translated this text.)

Today, it is almost impossible to avoid using Copilot & Grammarly for language and grammar editing of single sentences. ChatGPT has been used to improve a few paragraphs, but not for generating text from scratch. I have also tried out Wayless, a start-up in Lund, using PubMed to provide sourced summaries on specific research queries (*ChatGPT*, 2025; *Grammarly*, 2025; *Microsoft Copilot*, 2025; *Wayless*, 2025).

Ethical Considerations

Since all papers in this thesis are based on databases with retrospective data, the ethical issues are expected to be limited. This is because the research process does not impact the current care of the patients, and there is no physical or mental harm to them. However, several aspects still require attention. My considerations, which have also been presented in the applications for ethical approval, are on different levels: societal level, patient level, and data level.

Societal level

Will these studies lead to an improvement in overall health? I want to say yes without a doubt, but the world is not that easy. Ethical experts may argue that research with no valid outcome should not be performed at all, but the resources should be invested in other areas. Could I be sure to get a valid outcome?

Is the data reliable? As will be presented in the discussion, I have encountered several data issues that could impact the results and interpretation of these studies. Although I have invested much time in validating the data, I still cannot be sure that there are no serious flaws.

Should the research therefore not be done? Hopefully, the results will guide future revisions of guidelines concerning the treatment of pneumonia and antibiotic stewardship. Also, the research on the consequences of COVID-19 can be important for future crises.

Individual level

At the individual level, the risk of ethical problems related to the right to privacy is low compared to interventional studies, as we only used retrospective data. The personal identification numbers are pseudonymised to make it hard to identify individuals by chance. Still, if you have access to parallel systems such as EMR, it would be possible to identify individuals. However, the Patient Medical Records Law (*Patientdatalagen*) only admits access to EMR when you have direct care of the patient.

In Paper III, we studied the physicians' antibiotic prescribing habits. When the data was collected, it was possible to identify them. Information about sex and birth year was added. In the next step, their codes were changed to a pseudonymised code, and the key was destroyed. When the data have subsequently been processed, they are unlikely to be identified.

The data will only be presented on an aggregated level, where there is no risk of identifying the individuals. Thus, the findings have no direct benefit to participating individuals but only on the societal level.

Data level

At the data level, the dataset needs to be kept inaccessible to others, except for the researchers. We achieve that since the database is only accessible through a personal secure login. The personal identification numbers are pseudonymised, and the key is only available at Statistics Sweden until the end of the data collection. The researchers have no access to this key. The result will only be presented on an aggregated level. The risk of data leakage should be low.

In my opinion, the risk of low data validity poses a greater ethical threat. If the data is incorrect or has different flaws, the research result will not be valid and could be misleading. Therefore, it is essential to do a thorough check of the datasets to verify that they are valid and reliable.

Results

Introduction

I have chosen to present the results in key points, organised in an overall logical order. For each key point, I present the supporting results. In some cases, I present data from both databases, i. e. the KIDPC database used in papers I-III and the SSD database used in paper IV.

In the results section, the early period refers to 2006-2014, using the KIDPC database, and the later period refers to 2018-2021, using the SSD database. An infection visit is defined as a physician visit with at least one ICD-10 diagnosis code that could be interpreted as an infection[10]. Antibiotic prescription rate is defined as the number of prescriptions divided by the number of infection visits.

General reduction of antibiotic prescribing (Paper I)

During the early period, we observed no trends in the total physician visit rate for infections. A maximum of 469 visits per 1000 inhabitants was reached in 2011, and a minimum of 398 visits in 2014. We observed no trend in visit rate by sex, although female patients had more infection visits than male patients (58% were female during the early period).

[10] The following ICD-10 codes were used: A00-B99, G01-G05, G61, G93.3, H00-H01, H04.3, H10, H60, H65-H66, H70,H72, I30-I31, I33.0, I38, 140, J01-J06, J09-J18, J20-J22, J31-J32, J34.0, J36-J37, J40-J44, J47, K25-K26,K57, K61, K81, L00-L05, L08, L30.3, L60.0, L70-L73, L89, L97-L98, M71.0, N10, N12, N30, N34, N39, N41, N45, N48.1, N70-N73, N75-N76, O86, O91, P38, P39.1, R05, R36, R56, & T15. Details are available in the supplementary data of paper I.

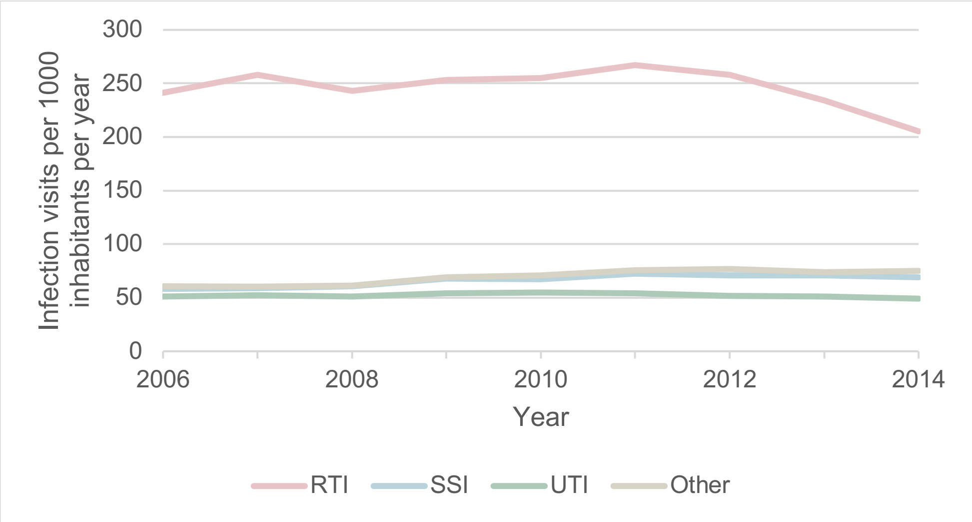


Figure 8A. Infection visits in primary care in the Kronoberg region 2006-2014 per 1000 inhabitants per year by infection group
RTI – Respiratory Tract Infections; SSI – Skin & Soft Tissue Infections; UTI – Urinary Tract Infections; Other – Other Infections.
Source: Paper I.

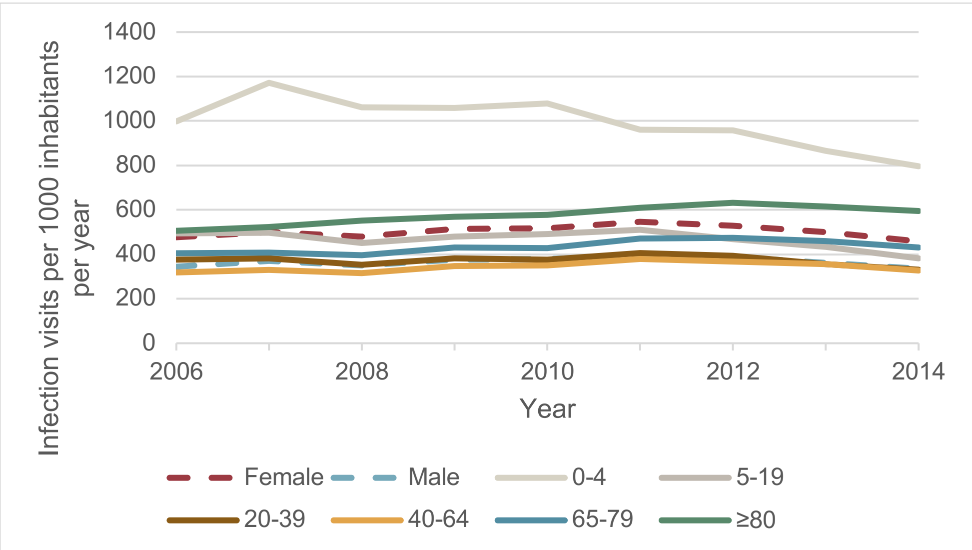


Figure 8B. Infection visits in primary care in the Kronoberg region 2006-2014 per 1000 inhabitants per year by sex and age group
Source: Paper I.

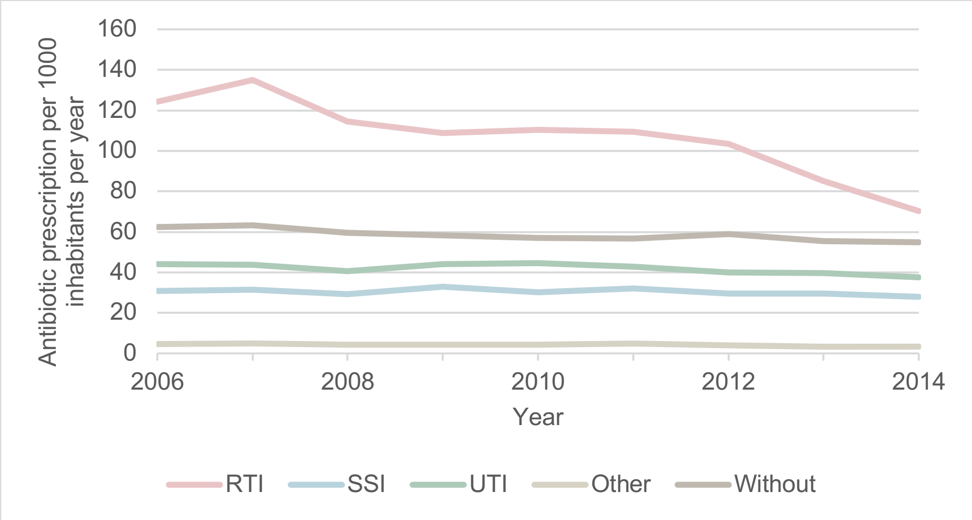


Figure 9. Antibiotic prescriptions in primary care in the Kronoberg region 2006-2014 per 1000 inhabitants per year by infection group
RTI – Respiratory Tract Infections; SSI – Skin & Soft tissue Infections; UTI – Urinary Tract Infections; Other – Other Infections; Without – Without Infection Visit.
Source: Paper I.

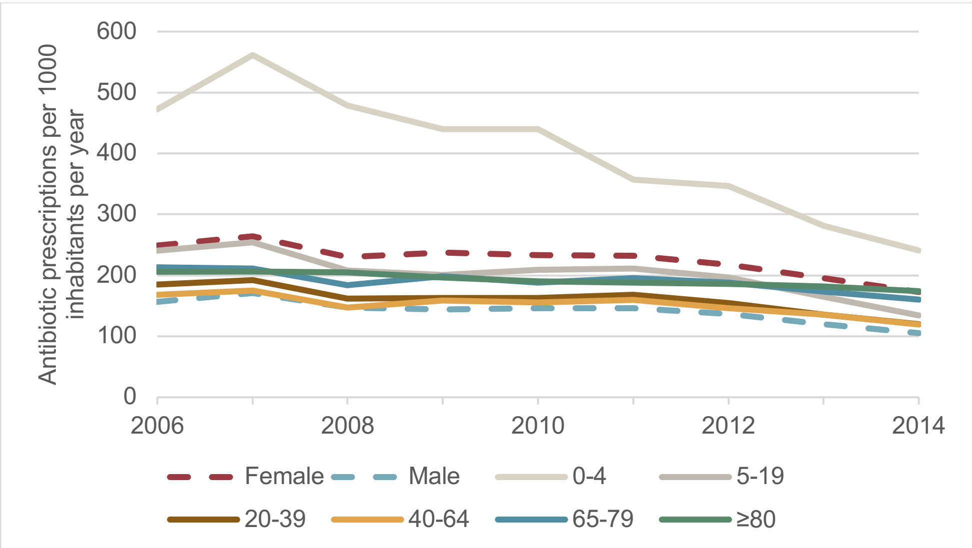


Figure 10. Antibiotic prescriptions in the Kronoberg region 2006-2014 per 1000 inhabitants per year by sex and age groups
Source: Paper I.

During the early period, children 0-4 years and adults over 80 years had the highest visit rates, 995 and 576 per 1000 inhabitants per year, respectively. The visit rate decreased in children 0-4 years during the early period, which was partly compensated by an increased visit rate in adults 65-79 years and adults over 80 years (Figures 8A-8B).

In contrast, we found that the antibiotic prescription rate decreased significantly during the early period from 266 prescriptions per 1000 inhabitants per year in 2006 to 194 prescriptions in 2014. We found no difference by sex; however, the decrease in antibiotic prescription rate was more pronounced in children aged 0-4 years (9% fewer antibiotic prescriptions per year) and in children aged 5-19 years (6% fewer per year). The antibiotic prescribing rate decreased mainly for RTIs (6% fewer antibiotic prescriptions per year), explaining 76% of the total reduction. Antibiotic prescriptions for UTIs also decreased (Figures 9-10).

During the early period, we were able to link 75% of the antibiotic prescriptions to an infection visit on the same day. Another 3% were linked to an infection visit within a week before the prescription, leaving 22% that could not be linked to an infection visit. These proportions were stable during the study period. We found that 36% of UTI antibiotics were prescribed without a diagnosis of infection, indicating that many UTIs are managed without a physician visit.

Most physicians reduced their antibiotic prescribing over nine years (Paper III)

In Paper III, we studied the physicians who had been active in the Kronoberg region for five to nine years. We found a general reduction in antibiotic prescribing for RTI per physician. After adjusting for the patients' age and sex, the mean ±SD adjusted prescribing rate for RTI per physician decreased from 45% ±16% during the first period to 35% ±13% during the third period. When comparing the first and third periods 84% (139/166) of the prescribers decreased their antibiotic prescribing rate (Figure 11).

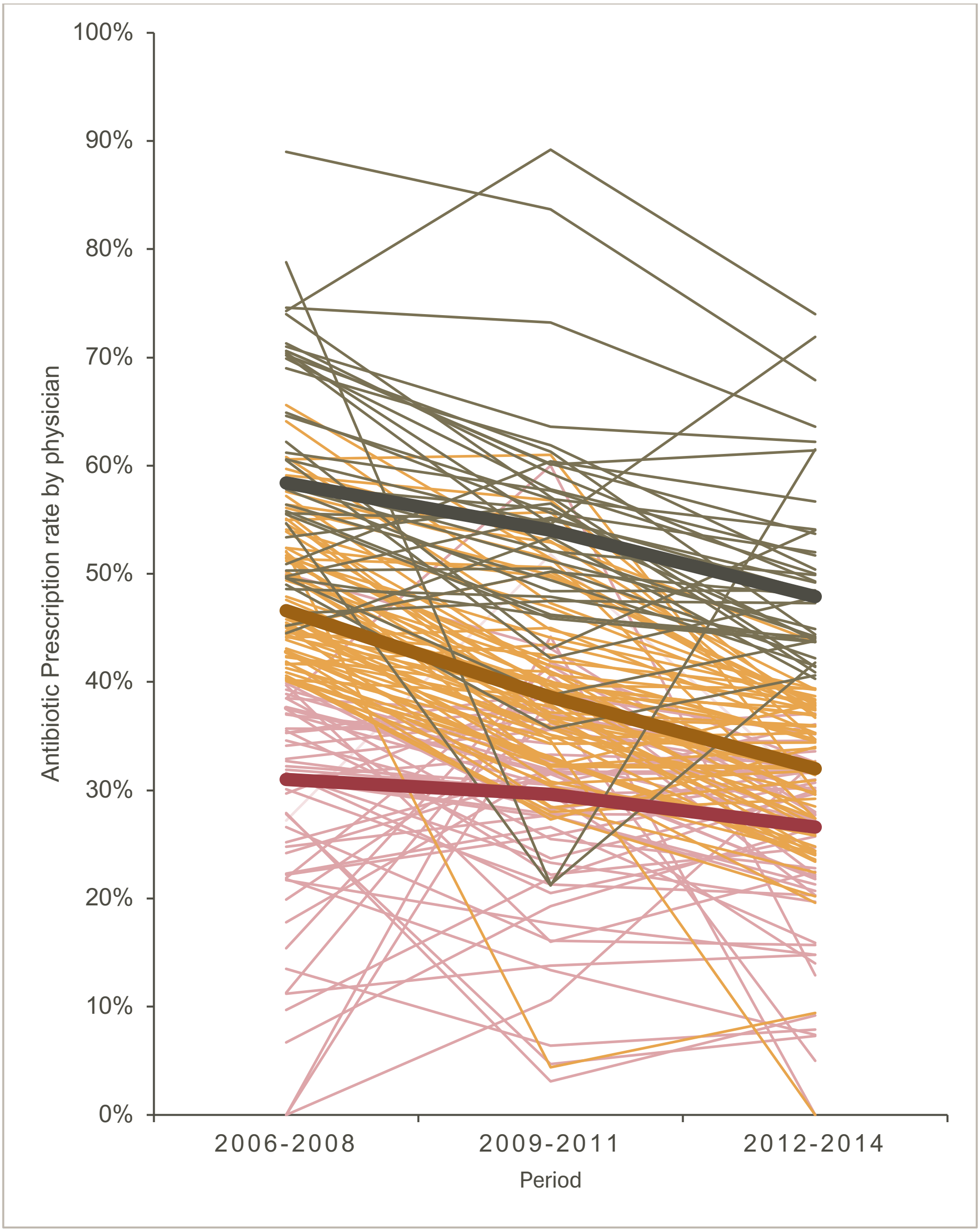


Figure 11. Change in antibiotic prescription rate by physician in the Kronoberg region 2006-2014
The olive green lines represent physicians in the High Prescribing Group, the orange lines represent physicians in the Decreasing Prescribing Group and the the rose lines represent physicians in the Low Prescribing Group. The dark green fat line is the median level for the High Prescribing Group, the brown fat line for the Decreasing Prescribing Group and the purple fat for the Low Prescribing Group. Source: Paper III and the KIDPC database.

Increasing use of point-of-care tests (Paper II)

In Paper II, we examined the use of diagnostic testing in LRTI during the early period from 2006 to 2014. Three diagnoses were evaluated: acute bronchitis (52% of the visits), pneumonia (25%), and cough (24%). More than 90% of the infection visits were made during the winter season (October-March). The prevalence varied between the years, with a peak in 2011, when the incidence of Mycoplasma infections was high (Figure 12).

During the later period, the incidence was affected by the COVID-19 pandemic; the incidence of both pneumonia and acute bronchitis (excluding COVID-19) dropped to approximately a half in 2020 and a third in 2021 of the pre-pandemic level.

During the early period, we observed an increase in the use of CRP testing, from 55% of visits in 2006 to 62% in 2014. For pneumonia patients, 71% had a CRP test, which was significantly more than in patients with acute bronchitis (62%). For both diagnoses, the use of CRP tests increased significantly during the period: pneumonia from 61% to 78% of the visits, and acute bronchitis from 53% to 66% (Figure 13). The median CRP value was 62 mg/L (IQR 27-107) for pneumonia patients and 11 mg/L (IQR 8-29) for acute bronchitis, and remained unchanged over time.

Low use of chest x-rays and microbiological testing for the diagnosis of pneumonia (Paper II)

In Paper II, we also studied the use of chest x-rays and microbiological testing in LRTI during the early period. Data was missing for 2006-2007. The use of chest x-rays increased significantly from 6.8% in 2008 to 9.4% in 2014. The increase was seen in patients diagnosed with acute bronchitis and cough, but not in patients with pneumonia. When a chest x-ray was performed for patients with pneumonia or acute bronchitis, CRP was analysed in 81% of the cases. Although there was an increase, the use of chest x-rays was still low.

Also, we found that microbiological testing increased from 1.8% in 2008 to 5.1% in 2014 for patients with pneumonia, and from 1.5% to 4.1% during the same period for patients with acute bronchitis. The most common analyses were the nasopharyngeal PCR test for *Mycoplasma pneumoniae* (2.5%), and bacterial culture (0.9%). Although there was an increase in microbiological testing, the level remained low.

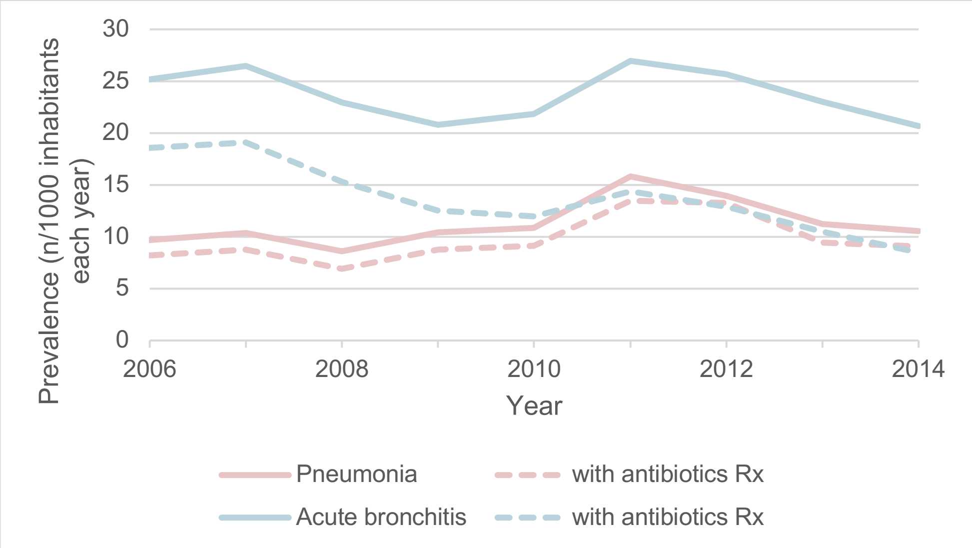


Figure 12. Prevalence (n/1000 inhabitants each year) of pneumonia and acute bronchitis, and antibiotics prescribed in patients aged 18–79 years in primary care in the Kronoberg region 2006-2014

Source: Paper II.

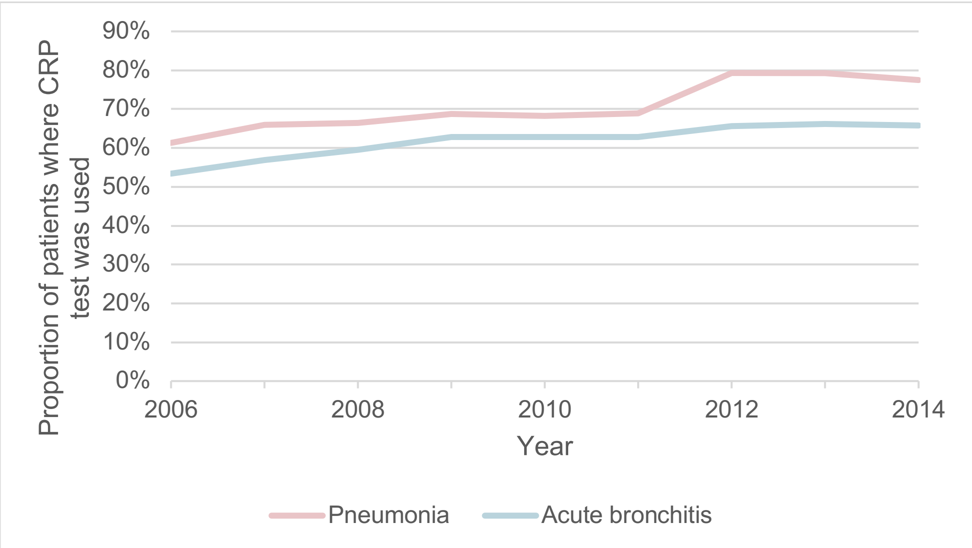


Figure 13. Proportion of patients aged 18–79 years with pneumonia and acute bronchitis in primary care in the Kronoberg region 2006-2014, where C-reactive protein (CRP) tests were used in the diagnostic process.

Source: Paper II.

Table 4. Comparison at group level between the prescriber groups of the use of diagnostic tests and the interpretation of the result in the Kronoberg region 2006-2014.
CRP – C-reactive Protein, GAS – Group A Streptococci, RADT – Rapid Antigen Detection Test. Potential bacterial diagnoses – acute media otitis, pharyngotonsillitis, pneumonia, and sinusitis. Source: Paper III.

Action	Low Prescribing Group	Decreasing Prescribing Group	High Prescribing Group	p value	Cramer's V
Order CRP test	36%	39%	44%	<0.001	0.06
CRP test result, median level for prescribing antibiotics	45	33	23		
Order RADT for GAS	16%	19%	26%	<0.001	0.09
Prescribing antibiotics when RADT for GAS is negative	15%	22%	35%	<0.001	0.18
Make a potential bacterial diagnosis	32%	37%	49%	<0.001	0.13

Interpretation of diagnostic testing explains differences in antibiotic prescribing levels (Paper III)

In Paper III, the focus was to compare physicians with different prescribing patterns. We divided the physicians who had been active during the early period 2006-2014 into three different groups described before: The High Prescribing Group (41 physicians), the Low Prescribing Group (52 physicians) and the Decreasing Prescribing Group (68 physicians) (Table 4). We then analysed if there were any differences concerning characteristics, use of point-of-care testing or selection of diagnoses.

Characteristics of the physicians

First, we studied the characteristics of the physicians. When we compared the three prescriber groups, the only significant difference was the frequency of RTI visits, which was lower in the Low Prescribing Group. We found no significant differences in physicians' sex, birth year, training level, continuity, and OOH work.

Point-of-care testing

Second, we studied the point-of-care testing at the index visits. At the group level, the Low Prescribing Group used CRP tests in 36% of the index visits, the Decreasing Prescribing Group in 39% and the High Prescribing Group in 44%. The use of CRP tests increased significantly from 37% during the first period to 43% during the third

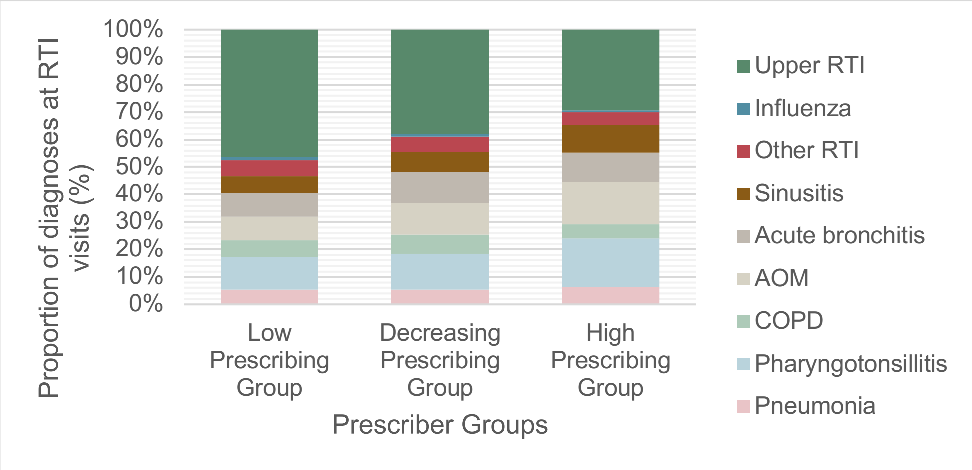


Figure 14. Proportion of diagnoses (%) for respiratory tract infections at the index visits by prescriber groups (the Low Prescribing Group, the Decreasing Prescribing Group and the High Prescribing Group) in the Kronoberg region 2006-2014
The diagnoses in this figure are ranked from high likelihood of viral aetiology (top) to potential bacterial aetiology (bottom).
Source: Paper III.

period. The High Prescribing Group prescribed antibiotics at a significantly lower CRP level (median 23 mg/L, IQR 6-53) than the other groups: the Decreasing Prescriber Group (median 33 mg/L, IQR 10-67) and the Low Prescribing Group (median 45 mg/L, IQR 15-82). A similar but non-significant result was seen when limiting to index visits with a diagnosis of pneumonia.

At the group level, RADT for group A streptococci (GAS) were used in 16% of the index visits in the Low Prescribing Group, 19% in the Decreasing Prescribing Group, and 26% in the High Prescribing Group. Almost all (95%) of cases with positive RADT received antibiotics. Patients with a negative RADT also received antibiotics in some cases: 15% in the Low Prescribing Group, 22% in the Decreasing Prescribing Group, and 35% in the High Prescribing Group ($p<0.001$, Cramer's V 0.18). The result was also significant when limiting to index visits, resulting in a diagnosis of pharyngotonsillitis.

Diagnoses

Third, at the group level, the diagnosis code for upper RTI was selected as the index visit in 46% of the Low Prescribing Group, 38% in the Decreasing Prescribing Group, and 29% in the High Prescribing Group ($p < 0.001$, Cramer's V = 0.13). An opposite pattern was seen for pharyngotonsillitis, acute media otitis and sinusitis, where the diagnoses were more frequent in the High Prescribing Group (Figure 14).

Comparison at the physician level

At the individual physician level, we observed a pattern similar to that at the group level. Physicians belonging to the High Prescribing Group used antibiotics at lower median CRP values and treated more patients with negative RADT for GAS with antibiotics. They were also more likely to select a diagnosis with potential bacterial aetiology.

Comparison of the Decreasing Prescribing Group and the High Prescribing Group

Ultimately, we aimed to investigate factors that are important for belonging to the Decreasing Prescribing Group compared to the High Prescribing Group. In a multiple regression model, we included the physicians' age, sex, and continuity, as well as the variables that emerged as significant in the groupwise comparison. We analysed odds ratios for belonging to the High Prescribing Group compared to the Decreasing Prescribing Group. Two variables remained significant in the adjusted model: Physicians in the High Prescribing Group were more likely to select a diagnosis with potential bacterial aetiology (aOR 1.32, 95% CI 1.14–1.52) and to prescribe antibiotics to patients with negative RADT for GAS (aOR 1.08, 95% CI 1.02–1.14).

Penicillin V was comparable to amoxicillin in the treatment of pneumonia (Paper IV)

In Paper IV, we compared penicillin V (PcV, phenoxymethylpenicillin) to amoxicillin, doxycycline, and other antibiotics in primary care as the outpatient treatment of community-acquired pneumonia during the later period 2018-2021. We included 34,306 cases of pneumonia in primary patient care treated with antibiotics among children >5 years old and adults, after excluding patients with chronic pulmonary disease or those receiving dose-dispensed medication. Among the included cases, 58% were treated with PcV, 6.9% with amoxicillin, 29% with doxycycline, and 6.9% with other antibiotics.

The primary outcome was hospitalisation for LRTI or all-cause mortality days 1-28. It occurred in 1115 cases (3.3% of all cases) and was highest in cases treated with amoxicillin (4.9%) and lowest in cases treated with doxycycline (1.9%). We found no differences between amoxicillin and PcV for the outcome of hospitalisation for LRTI or all-cause mortality in the adjusted logistic regression model with all cases (aOR 1.07, 95% CI 0.87-1.32). However, we found that doxycycline (aOR 0.53, 95% CI 0.45–0.63) showed a lower risk than PcV for the primary outcome. Additional sensitivity analyses of subgroups, including pre-pandemic, pandemic, children aged 5-19 years, adults, tobacco use, obesity, Region Skåne, and other regions, showed similar results.

We also analysed all-cause mortality for days 1-28 separately. It occurred in 157 cases (0.46% of all cases) and was highest in cases treated with amoxicillin (37 events, 1.6% of amoxicillin-treated cases). The odds ratio for all-cause mortality was higher with amoxicillin than with PcV, doxycycline or other antibiotics in all the regression models.

A secondary outcome was antibiotic switch, which occurred in 3825 cases (11% of all cases), with the highest rate in cases treated with PcV (14% of PcV-treated cases) and the lowest in cases treated with doxycycline (5.3% of doxycycline-treated cases). Doxycycline was also the most common secondary antibiotic treatment. Cases treated with amoxicillin, doxycycline, and other antibiotics compared to PcV showed a lower rate of antibiotic switch.

We analysed the CRP test as a measure of disease severity. At day 0, CRP measurements were reported in 71%, not ordered in 24%, and missing due to incomplete data in 5% of all cases. The CRP result was >50 mg/L in 64% of the performed tests. There was a significant difference in the proportion of CRP >50 mg/L depending on antibiotic treatment. In cases treated with PcV, 73% of CRP tests had CRP >50 mg/L compared to 48% of CRP tests in cases treated with doxycycline ($p<0.001$, Cramer's V 0.28). Subgroup analyses for pneumonia cases with CRP >50 mg/L showed similar results for amoxicillin compared to PcV (aOR 0.97, 95% CI 0.74–1.28) for the primary outcome hospitalisation for LRTI or all-cause mortality.

During the early period, when narrow-spectrum antibiotics (PcV and amoxicillin) were prescribed for patients with pneumonia, the median CRP value was higher (72 mg/L) compared to when broad-spectrum antibiotics (doxycycline and erythromycin) were prescribed (50 mg/L) ($P<0.001$).

No excess antibiotic prescribing during out-of-hours (Paper I)

In Paper I, we studied antibiotic prescribing during out-of-hours (OOH) services during the early period 2006-2014. The OOH infection visits decreased from 65 visits per 1000 inhabitants in 2006 to 43 visits in 2014. Also, the antibiotic prescribing decreased from 43 prescriptions per 1000 inhabitants in 2006 to 26 prescriptions in 2014.

The proportion of diagnoses comparing IH to OOH is shown in Figure 15. In total, 12% of all visits were during OOH. RTIs were the most common diagnoses during both IH and OOH. However, acute otitis media, pharyngotonsillitis, and lower UTIs were more common during OOH. A total of 15% of all antibiotics were prescribed during OOH. The likelihood of receiving an antibiotic prescription was 55% during OOH visits compared to 41% during IH visits, suggesting a relative over-prescribing rate of 37% during OOH. When we adjusted for age, sex, and diagnosis, the over-prescribing rate during OOH was 9% compared to IH. Age and sex adjusted relative risk of antibiotic prescribing during OOH per diagnosis was significantly higher for acute otitis media, pharyngotonsillitis, pneumonia, SSI and UTI.

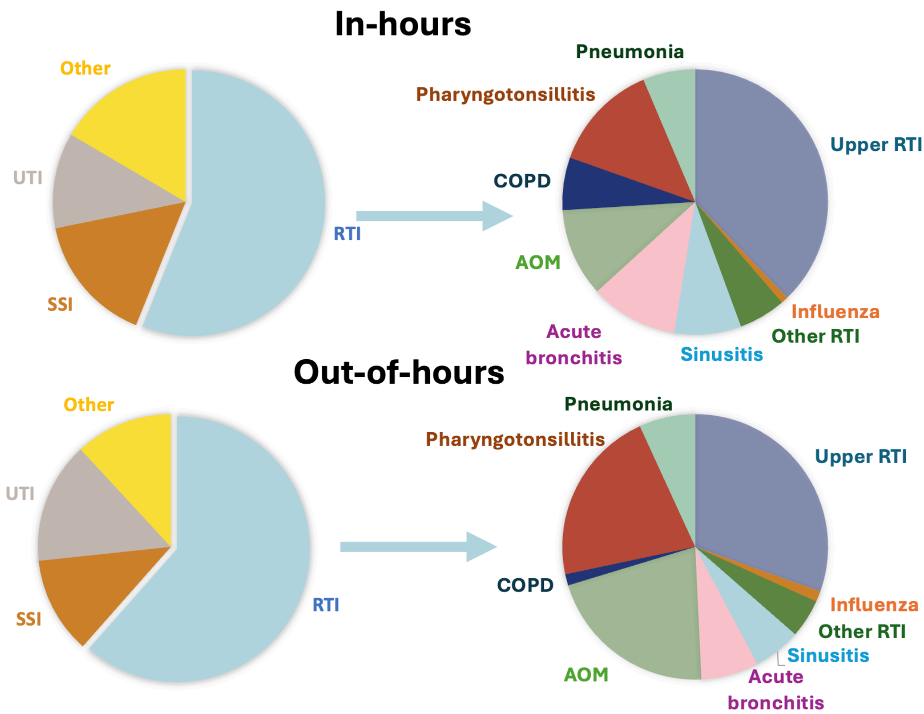


Figure 15. Proportion of diagnoses by infection groups (left) and for RTIs by infection diagnoses (right) comparing in-hours (top) with out-of-hours (bottom) in the Kronoberg region 2006-2014
AOM – Acute Otitis Media, COPD – Chronic Obstructive Pulmonary Disease, RTI – Respiratory Tract Infections, SSI – Skin & Soft Tissue Infections, UTI – Urinary Tract Infections.
Source: Paper I.

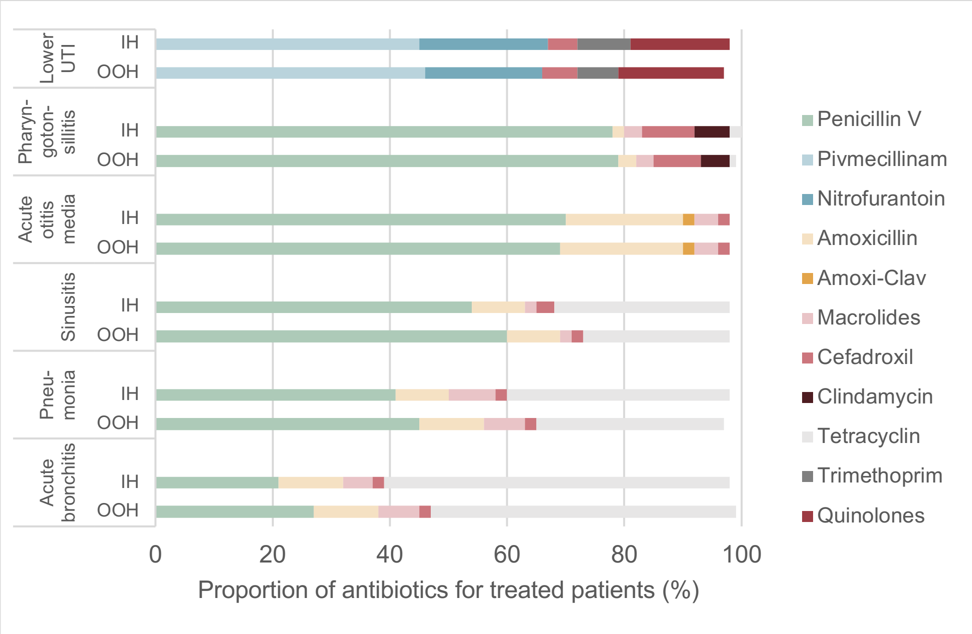


Figure 16. Antibiotic treatment for the six most common diagnoses in-hours compared to out-of-hours in primary care in the Kronoberg region 2006-2014
Penicillin V, Phenoxymethylpenicillin; UTI, Urinary Tract Infection.
Source: Data from the KIDPC database.

No excess prescribing of broad-spectrum antibiotics during out-of-hours (Paper I)

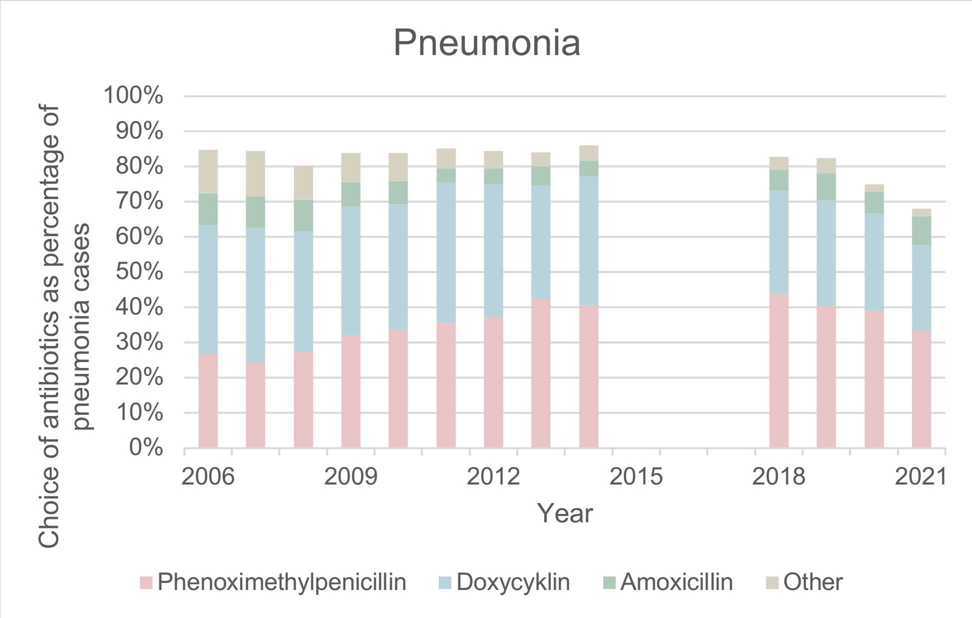
In Paper I, we also compared OOH to IH concerning the relative use of different antibiotics for the six most common diagnoses during the early period 2006-2014. The prescription rate was higher during OOH for pneumonia, acute otitis media, and pharyngotonsillitis. The relative use of narrow-spectrum antibiotics was higher during OOH. Although the difference was statistically significant, the treatment choices for each diagnosis were comparable between IH and OOH prescriptions (Figure 16).

Fewer antibiotics in acute bronchitis (Paper II)

In Paper II, we studied antibiotic prescribing to patients diagnosed with LRTI during the early period. We found that the antibiotic prescription rate for patients with pneumonia was 84% overall and did not change (OR 1.11; 95% CI 0.89-1.38). For patients with acute bronchitis, the antibiotic prescription rate decreased from 74% in 2006 to 41% in 2014 (OR 0.25; 95% CI 0.22- 0.28). See Figure 17.

Additionally, we found that the proportion of PcV prescribed for pneumonia patients increased (OR 1.9; 95% CI 1.6-2.3), while the use of amoxicillin and erythromycin decreased ($p < 0.001$), and the proportion of doxycycline prescribed remained unchanged ($p = 0.74$).

In Paper IV, we studied pneumonia in four regions. The data subset of the Kronoberg region showed similar proportions of antibiotic choice during the pre-pandemic period 2018-2019 as during 2013-2014, with a slight decrease in the proportion of treated cases during the pandemic period 2020-2021. Data from the SSD database showed that the decrease in cases of acute bronchitis seen during the early period continued during the later period.



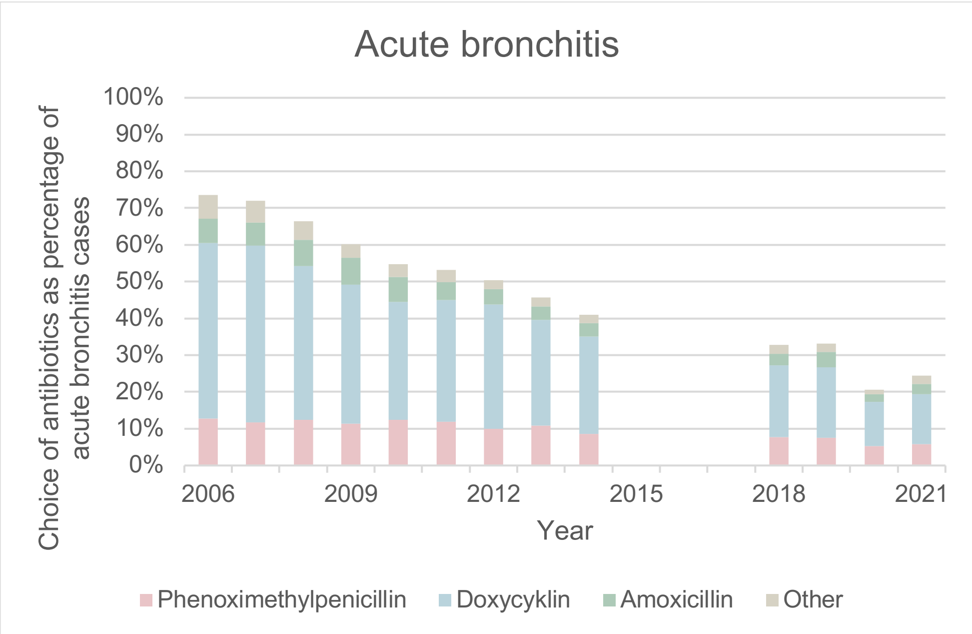


Figure 17. Distribution of antibiotic prescriptions for pneumonia and acute bronchitis in patients aged 18–79 years in primary care in the Kronoberg region 2006-2021
Source: Paper II provided data for 2006-2014. Paper IV and the SSD database provided data for 2018-2021.

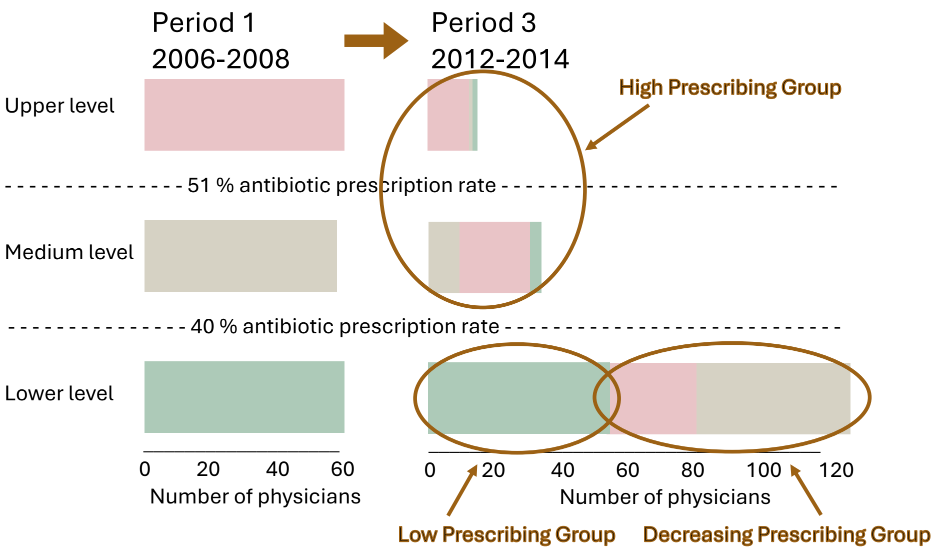


Figure 18. Change in physicians' antibiotic prescription rate between 2006-2008 and 2012-2014 in the Kronoberg region
The colours represent the prescribing level during period 1 where rose is high prescribers, grey is medium prescribers, and green is low prescribers and where their positions were during period 3. The High Prescribing Group is represented by the physicians who remained at the upper or medium level (the five physicians who initially were at the lower level were excluded). The Decreasing Prescribing Group consisted of physicians who decreased their prescribing levels from upper or medium to lower levels. The Low Prescribing Group were the physicians who remained at the lower level.
Source: Paper III.

Nine out of ten low prescribers remained low prescribers (Paper III)

In Paper III, we examined whether physicians change their antibiotic prescribing habits over time regarding RTIs during the early period of 2006-2014. Out of 55 low-prescribing physicians during the first period, 2006-2008, 50 remained low-prescribing during the third period, 2012-2014 (Figure 18).

The means ±SD of antibiotic prescribing rate for the physicians of the Low Prescribing Group during the three periods were 27 ±11, 29 ±11, and 24 ±9, respectively. Thus, the change was small compared to the two other prescribing groups.

Table 5. Comparison at group level between the prescriber groups of the effects after the index visit in primary care in the Kronoberg region, 2006-2014.

Source: Paper III.

Effect	Low Prescribing Group	Decreasing Prescribing Group	High Prescribing Group	p value	Cramer's V
Return visit within 30 days	14%	14%	15%	<0.001	0.009
Return visit within 30 days if no antibiotics at index visit	16%	16%	16%	0.64	0.003
Antibiotics at return visit within 30 days	42%	43%	44%	0.015	0.016
Antibiotics at return visit within 30 days if no antibiotics at index visit	43%	42%	45%	0.007	0.024

Seeing a low-prescribing physician did not result in more return visits or secondary antibiotic prescriptions (Paper III)

In Paper III, we also examined what happened with the patients after seeing a physician, depending on the physician's prescribing group belonging. We found that return visits within 30 days occurred more often after seeing a physician from the High Prescribing Group (15% of the visits compared to 14% for the other prescriber groups). If antibiotics were prescribed at the index visit, return visits occurred in 16% of index visits in all prescribing groups (Table 5).

The same pattern was observed regarding the risk of repeat antibiotic prescriptions. Antibiotics were prescribed at a return visit, slightly more often in the High Prescribing Group. If no antibiotics were prescribed at the index visit, the risk of receiving antibiotics at a return visit was slightly higher in the High Prescribing Group (Table 5).

General reduction of respiratory tract infections during the COVID-19 pandemic (Paper IV)

In Paper IV, we also analysed the change in pneumonia incidence in primary care during the COVID-19 pandemic. We found that the number of pneumonia cases decreased from 5.9 per 1000 inhabitants per year during the pre-pandemic period 2018-2019 to 2.7 cases in 2020 and 1.6 cases in 2021. There were small but significant changes in treatment choice during the pandemic. The proportion of pneumonia cases treated with PcV decreased from 58% before to 56% during the pandemic, while cases treated with amoxicillin and doxycycline increased (from 6.6% to 7.6%, and from 28% to 30%, respectively). The number of pneumonia cases that were hospitalised for LRTI or died from any cause was 43% lower in 2020-2021 compared to 2018-2019, while the proportion of pneumonia cases that were hospitalised or died increased from 2.8% before to 4.4% during the pandemic. The proportion of antibiotic switches decreased from 11% before to 10% during the pandemic.

The reduction of infections during the COVID-19 pandemic was mainly due to a lower incidence of RTI (167 cases per 1000 inhabitants per year 2018-2019, 112 cases per 1000 inhabitants per year 2020-2021) while the incidences of SSI & UTI remained unaffected. The reduction in infections was observed across all age groups, but was most pronounced in children <5 years (638 cases per 1000 inhabitants per year in 2018-2019, and 381 cases per 1000 inhabitants per year in 2020-2021) (unpublished data, the SSD database). During the early period 2006-2014, the incidence of RTI was higher (246 cases per 1000 inhabitants per year), and the incidence of infections in children <5 years was higher (995 cases per 1000 inhabitants per year).

In line with the reduction in infections, we also observed a decrease in antibiotic prescribing during the pandemic. Antibiotic prescriptions for RTI decreased from 61 prescriptions per year 2018-2019 to 27 prescriptions per year 2020-2021, while prescriptions for SSI and UTI were stable. Again, the reduction was seen in all age groups but was most pronounced in children <5 years (from 254 antibiotic prescriptions per year in 2018-2019 to 118 per year in 2020-2021) (unpublished data, the SSD database). During the early period, antibiotic prescriptions were also high for RTI (107 prescriptions per year), and in children <5 years (402 prescriptions per year).

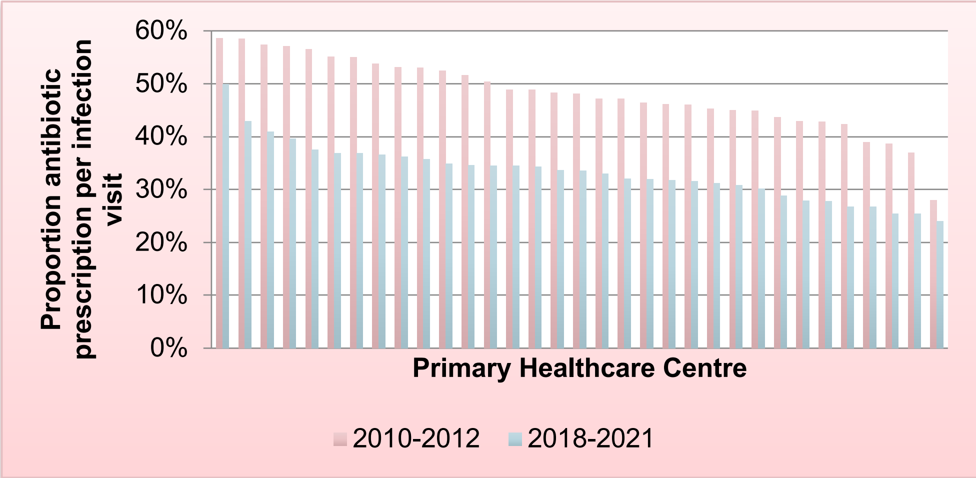


Figure 19. Variation in antibiotic prescribing per primary health care centre (PHCC) in the Kronoberg region 2010-2012 and 2018-2021
Proportion of antibiotic prescriptions per infection visits per PHCC. NB! The PHCCs are not pairwise matched, since the first dataset is anonymous. Infection visit was defined as a visit with at least one of the following ICD-10 codes: B34, H65-H66, J01-J05, J09.9, J11, J18, J22, J36, J42, J44.1, L01-L05, L08, & R05.
Source: The Kronoberg region for the period 2010-2012 and the SSD database for the period 2018-2021.

Variability

To compare the variability in 2010-2012 with that in 2018-2021, we used the same diagnosis codes, even though the code for upper RTI (J06 – "*Övre luftvägsinfektion*") was missing. Since the PHCCs and the physicians in the first dataset were anonymised, we could not compare each PHCC or each physician individually. Furthermore, in the 2010s, many physicians retired. Between 2010 and 2012, the mean ±SD antibiotic prescribing rate was 48% ±6.8%. Between 2018 and 2021, the mean was 33% ±5.4%.

A similar pattern was seen on the individual physician level when analysing physicians with, on average, more than 25 infection visits a year. Between 2010 and 2012, the mean antibiotic prescribing rate was 50% ±13%, and for the later period, the mean was 33% ±13%.

Figure 19 shows that even though the antibiotic prescription rate is lower during the later period, there is still a variability.

Discussion

Main findings

- Antibiotic prescribing decreased from 2006 to 2014, particularly among children and in respiratory tract infections, although the infection visit rate remained stable.
- When adjusted for sex, age groups, and diagnoses, the antibiotic prescription rate was slightly higher at out-of-hours visits compared to in-hours visits.
- There was an increase in the use of diagnostic testing (the CRP test and microbiological tests), although at a stable rate of LRTI.
- Low prescribers stayed low prescribers. The characteristics of high prescribers were not different from those of other prescribers; however, the behaviour of high prescribers promoted antibiotic prescribing.
- Treating community-acquired pneumonia with PcV compared to amoxicillin posed the same risk of hospitalisation for LRTI or all-cause mortality, while antibiotic switches were more common with PcV.

Methodological considerations

Real-world data (RWD)

In Sweden, there is no national system for primary care health data, but the RWD is available at the regional level. This means that even if you have obtained ethical approval, you still need to obtain approval from each region to receive data for research purposes. Also, the juridical interpretation of the Patient Data Law differed between the regions.

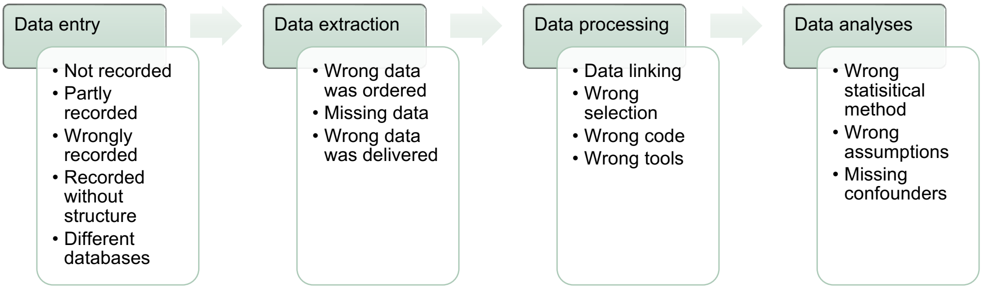


Figure 20. Potential problems with real-world data.

Several prerequisites must be met to use RWD. First, you need to know how data is registered and how complete the dataset is. Second, you need to order an extract of an appropriate dataset from the data source, for example, the care provider. You have to limit the dataset without missing valuable data. Third, you need to process the data and verify that you have received what you expected. Fourth, you need to analyse the data with the correct assumptions, using the appropriate statistical methods, and adjust for confounders if possible. In this section, we describe some of the challenges we encountered while working with RWD (Figure 20).

Data entry

In Sweden, all regions are using separate EMRs with different configurations. We need to know what data is available, how it was entered and if there are any apparent missing data (Table 6).

Data extraction

When we ordered the dataset, we asked for a defined population that we wanted to extract. Then we asked for "all" data that could be relevant for this population. If you need to limit your dataset, it is better to do it yourself when you can control the limitation process. Still, we encountered problems with the dataset's limitations by mistake (Table 6).

Table 6. Problems with data entry and data extraction of real-world data that we have encountered during our work with the KIDPC and the SSD databases

Type of data	Problems	Solution
Diagnose codes	Primary and secondary care had different coding systems. Sometimes, only the primary diagnosis is reported and not all diagnoses.	Check for both common and uncommon codes. Determine how to manage primary and secondary diagnoses. Decide how to handle if two infection diagnoses are made at the same visit, for example, otitis and upper RTI, or cough and pneumonia.
Contact codes	The system connects all activities at one visit with a contact code. However, this code is often incorrect.	It is generally better to link the data by personal ID, clinic, and date.
Laboratory analyses	There could be more than one name for an analysis if the laboratory has changed the test provider or the method. Point-of-care analyses are often handled differently and registered at the local laboratory. We found that during the first years, the CRP measurements at the OOHCs were written on paper and not recorded in the laboratory system.	Careful mapping of laboratory analyses. If sudden increases or decreases in the incidence of an analysis, try to verify if it is a true change or just missing data.
Microbiology analyses	Different laboratories may have different name structures, such as “Material: urine, Test: general culture” or “Test: Urine culture”. The naming principles may change over time. There is usually more than one answer: preliminary result, final result. The result text is often non-structured and requires interpretation: positive or negative, growth of 1-6 bacteria, and analysis of resistance patterns.	Careful mapping of microbiological results from different regions.
Radiology investigations	The names of the radiology investigations may vary over time and between units. The result field is non-structured and requires interpretation. If the order date and the result date are the same, it is likely to be an emergency investigation.	Manually classify the results into groups of clinical findings.
Pharmacology data	There are several different data sources: the prescribed medication noted in the EMR, the prescription for the pharmacy in the EMR linked to a disease or not, and the collected medicines at the pharmacy. Sometimes, there is more than one prescription on the same day, making it unclear which medication is relevant. Some patients are receiving dose-dispensed medicines, which are registered in a separate database and can easily be overlooked.	Depending on what pharmacology data you need, decide which database is most appropriate, and understand the limitations of the chosen database.

Table 6 continued.

Type of data	Problems	Solution
Manually entered data	Some point-of-care tests are entered manually, which carries a risk of entering the wrong number or in the wrong field. For example, a CRP test of 5.6 is likely to be a glucose value. They also need to be standardised, for example, 'neg', 'negative', and '0' could mean the same thing.	Decide how you should handle data that is outside a reasonable range.
Incomplete data delivery	The first delivery for the SSD database from one region contained only 75% of the expected cases of pneumonia. Erroneously, the dataset was limited because a non-compulsory flag was not set to ready.	Reorder data when the dataset is incomplete. If not possible, describe the problem and try to find solutions, for example, by limiting the study to areas where the dataset is complete.

Data processing

An important step is to link data. The personal identification number links individuals (except for visitors and asylum seekers) between data sources. Next, the date and the clinic could be used to link visits, but different date formats and different clinic names could pose problems (Table 7). McGuckin *et al.* describe challenges in answering four clinical questions with RWD. Three to six different data sources were needed to answer three of the questions. The fourth question required a paper chart audit. The challenges they encountered were whether the necessary data was available in the data sources, whether the data was complete and accurate, whether the number of visits for the condition could be measured, and whether relevant laboratory data was available (McGuckin *et al.*, 2022).

During data processing, we discovered that some data were missing and that we had to reorder them. For the last study, we aimed to incorporate a comorbidity score, and we selected the Swedish version of the Charlson Comorbidity Index (CCI). However, we found that this version missed most diabetes cases, which was the most common comorbidity. We had to adjust the script to include them (Table 7).

A Canadian study by Swaleh *et al.*, described the process of extracting quality indicators by linking data from different sources in four steps: project planning, information generating, limitation analysis of information, and finally action. The first two steps were an iterative process, where different solutions needed to be found. In limitation analysis, some clinical questions could be answered, some with limitations, and some not at all (Swaleh *et al.*, 2023). Our research process has similarities with this quality indicator process.

Table 7. Problems with data processing and data analysis of real-world data that we have encountered during our work with the KIDPC and the SSD databases

Type of data	Problems	Solution
Dataset verification	Although a clear order, the extracted dataset is rarely correct in the first run. When you get a large dataset, it is difficult to understand that something is missing.	Do simple frequency tables and cross tables. Compare the retrieved numbers with the expected numbers.
Data linking	Visitors and asylum seekers were excluded because of data linking problems. The date format varied across the data sources, and some included time. The names or identification of the clinics were not entirely identical.	Verify that the date format and clinic names are identical between data sources.
Changes in diagnosis codes	Although I knew I needed to update the code list of infections, I almost missed the code U07 for COVID-19 because U-codes had not been used for infections before. In some cases, ATC codes are registered as diagnosis codes, which had to be omitted.	Analyse which codes are used and select those relevant for your study.
Differences between datasets	In the KIDPC database, I used prescribed antibiotics from the EMRs. In the SSD database, I used the medication database of antibiotics collected from pharmacies. This medication database included dose-dispensed drugs where long-term use of antibiotics is registered as a new collected drug every second week.	Identify and describe differences between datasets. If possible, find ways to adjust for the differences.
Manually transcribed data	During data processing, it is sometimes necessary to transcribe data manually with the risk of transcription errors (Mickelsson *et al.*, 2025).	Decide how you should handle data outside a reasonable range.
Using valid tools	A Swedish version of the Charlson Comorbidity Index (CCI) contains a serious error. CCI is one of the commonly used comorbidity indexes (Quan *et al.*, 2005). A version adapted for Swedish coding is available (Ludvigsson *et al.*, 2021). From the diagnosis code lists, 17 disease groups are identified, and a score is calculated. I ran the Swedish version of CCI in the statistical software R. When I added the CCI data to my file of pneumonia cases, I noted several patients who, by mistake, were assigned aids. After contacting the author of the script, I learnt that he had implemented the original article correctly. However, an erratum corrected the aids error (Ludvigsson *et al.*, 2023). On the Karolinska web page, there was a link to a script adapted for this erratum. During the comparison of the Swedish CCI with the standard CCI, I noted that most cases of diabetes were missing due to the omission of the most common diabetes codes. I have written to the principal author that it is essential that this error be fixed (Jonas Ludvigsson, personal communication, 2024-25).	For paper IV, we have used a corrected version of the script that identifies the missing diabetes codes.
Choice of statistical method	For paper IV, we chose the population of all outpatient cases of pneumonia, but had to adjust to primary care cases only. We used binomial logistic regression, but had to add propensity score analysis for comparison. We had to adjust the confidence intervals for skewness with the robust sandwich estimator method. The propensity score analysis had to be described in detail with the calliper setting and replacement handling.	Use a step-by-step guide to select the statistical method, such as Laerd Statistics (Lund & Lund, 2025). Verify the chosen method with a statistician.

In another Canadian study of antibiotic prescribing, McIsaac & Kukan (2023) wanted to study whether there were differences in delayed prescribing and in the case mix, as high prescribers claimed. They chose to compare EMR with clinical records to verify the validity and found that EMR codes and clinical diagnoses were similar. Delayed prescriptions were common, but information about them was only available in the clinical records, so the EMR overestimated the antibiotic prescribing. We do not have access to information about delayed prescriptions, but we assume that it is rarely used.

Data analysing

When you plan a study, for example, the aims, the selection of the study population, the outcomes, and statistical methods should be decided in advance. However, during the research process, you may encounter problems which can prevent you from following your initial plan. Additionally, the review process of a submitted paper may require further analysis. An explorative study may have a larger degree of freedom than a randomised clinical trial. We tried to follow our initial plan, but in some cases, the plan has been adjusted. For paper IV, we initially studied all outpatient cases of pneumonia; however, during the review process, we were advised to limit the study to primary care patients only. Additionally, we had to add a propensity score analysis to confirm the results of the logistic regression (Table 7).

A special case was when we wanted to compare data from the early period 2006-2014 to the later period 2018-2021. To be able to do an accurate comparison, we needed to produce data in the same way for the later period as we did six years before for the early period. It was not entirely possible as the KIDPC database contained prescribed antibiotics from the EMRs, while the SSD database contained antibiotics collected at the pharmacies (Table 7).

Summary

To summarise, there are many methodological considerations with RWD. Although we hope that we have addressed all data problems in our datasets, we cannot rule out the presence of residual confounders. In a Lancet comment, Gerstein *et al.* (2019) argue that studies with RWD often yield relationships with relative risks between 0.5 and 2, and those are most susceptible to unaccounted-for confounding. Their solution is to combine randomisation with RWD follow-up.

The KIDPC database

A strength of the database was that the KIDPC database was complete for infection visits and antibiotic prescriptions in primary care in a region in Sweden. Because the whole region was included, the data were RWD without any selection due to study participation. Additionally, the same EMR system was used throughout the study period, thereby reducing the risk of information errors. All OOH infection visits and prescriptions were included, which enabled comparisons between IH and OOH. Because writing a diagnosis was compulsory for all visit records, very few diagnoses were missing. Also, there was no access to telehealth medicine during this period.

There are limitations with the KIDPC database. We have not validated the diagnoses by examining the EMR. We have not explored the reason why some antibiotics are prescribed without a coded diagnosis of an infection. Other antibiotics than oral and parenteral antibiotics (ATC code J01) are missing in the database, such as antibiotics in topical skin and eye preparations. We underestimate the antibiotic rate for the elderly (mainly over 80 years) due to partly missing data for patients with medication administered through the dose-dispensing system. We lack information on hospital referrals, which could be a reason for not prescribing antibiotics in primary care. Also, a follow-up visit after a hospitalisation could be coded with the primary infection diagnosis. This could explain the somewhat low antibiotic prescription rate in the pneumonia group. We were unable to measure the rate of delayed prescribing because we lacked access to pharmacy dispensing data.

The SSD database

The strength of the SSD database lies in its large, real-world dataset, which encompasses a quarter of the Swedish population. By linking consultations, diagnoses, and treatments from the EMRs of primary and hospital care and following patients over time, actual cases of different diseases can be identified to address the management and the outcomes of various treatments.

However, there are limitations. First, in clinical practice, diagnoses and treatment choices are based on physicians' judgments. The EMR extract could not provide information regarding the patients' clinical status, duration of symptoms, or disease severity. Some cases might have been misdiagnosed. We have not been able to validate the dataset towards actual patient records. Confounders such as smoking habits and obesity could only be identified if the patient had a diagnosis of tobacco use or obesity. Furthermore, confounders such as socioeconomic status were not accounted for. Finally, even though we have information on dose-dispensed medication, we can still miss short-term medications (e.g., antibiotics) that were taken from a local storage at the nursing homes.

Other databases

There was another primary care database with infection data from Sweden. The Primary Care Record of Infections in Sweden (PRIS) database (Tyrstrup *et al.*, 2016) consists of data between 2007 and 2013 on consultations with an infectious diagnosis and all antibiotic prescriptions from PHCCs, which voluntarily choose to participate on an annual basis. The data was linked and included information about age, sex, and laboratory results. This database had a larger dataset than the KIDPC database, but it only covered selected PHCCs in other regions and lacked OOH data.

Since 2023, there has been a national system for primary care quality in Sweden – *Primärvårdskvalitet*. The aggregated data is collected automatically, and quality indicators are presented. The aim is to facilitate nationwide benchmarking as a tool for quality improvement and research. The system is available for 97% of the PHCC in Sweden. Several indicators for infectious diseases have been developed in cooperation with the STRAMA organisation (Mansson *et al.*, 2025). Since the data is only available at an aggregated level, it is helpful in confirming data completeness but cannot be used for individual-level research.

Sweden has a national patient register that contains information on diseases and treatments in specialised care, but lacks information from primary care. In other countries with patient registers that contain information from primary care, research is possible by linking data with other databases, such as drug databases or cause of death databases.

In the United Kingdom, there is a long tradition of EMR software suppliers delivering data from PHCCs that opt in to primary care research databases, for example, Clinical Practice Research Datalink (CPRD), QResearch, The Health Improvement Network (THIN) database, and Optimum Patient Care Research Database (OPCRD) (Edwards *et al.*, 2023). Lately, the OpenSAFELY platform has been used to study common infections in primary care before, during and after the COVID-19 pandemic (Fahmi *et al.*, 2025). In Norway, a practice-based research network has been established in recent years, PraksisNett, which covers 10% of the population (Kristoffersen *et al.*, 2022).

There is also an interest in doing international comparisons, which is achieved through cooperation between research groups in different countries. One European example is the European Health Data & Evidence Network (EHDEN), which was established to address the heterogeneity of data capture methods, coding standards, and governance structures by building a data infrastructure that harmonises RWD (Blacketer *et al.*, 2025). One intercontinental example is INTRePID (International Consortium of Primary Care Big Data Researchers), which assembles primary care data from diverse sources across different countries spanning five continents (Westfall *et al.*, 2024).

General discussion

General reduction of antibiotic prescribing

The reduction in antibiotic prescribing seen during the early period (2006-2014) continued during the later period (2018-2021), and was similar throughout Sweden (Swedres-Svarm, 2025).

In the PRIS database, the visit rates per 1000 persons per year for infections during IH were 457 (in 2008), 441 (in 2010), and 406 (in 2013), which were similar to Paper I. Antibiotic prescribing decreased by 36% in the PRIS study and 27% in Paper I. Perhaps participation in the PRIS database could have triggered a more restrictive antibiotic prescribing behaviour compared to our real-world study.

The same pattern with a general reduction of antibiotic prescribing has been shown in studies from other countries, such as Norway (Haugom *et al.*, 2021; Larsen *et al.*, 2022; Skow *et al.*, 2023), Finland (Parviainen *et al.*, 2019), England (Bou-Antoun *et al.*, 2018) and Denmark (Kristensen *et al.*, 2019) during the same period, but not in Australia (Andersson *et al.*, 2022).

Several explanations are possible for the reduction in antibiotic prescriptions, but it is likely due to changes common to the different countries. One explanation is that the child vaccination program against *S. pneumococcus*. Additionally, there is likely to be an increasing awareness among the general public that antibiotics should be used only when necessary.

Infection visits and antibiotics were more common in women than in men. One common assumption is that women are more likely to experience UTIs. However, Smith *et al.* (2018) reported that women receive more antibiotics even if UTIs were excluded, and assumed that more infection visits in women lead to more antibiotic prescriptions.

In 2005, STRAMA, together with the government, launched a national strategy to prevent antibiotic resistance and healthcare-associated infections. Several actions have been performed in relation to this strategy. Diagnosis-specific guidelines for optimal antibiotic use have been published and promoted, and the use of antibiotics has been reported at the local, regional, and national level (Molstad *et al.*, 2017; Socialdepartementet Regeringskansliet, 2005). Between 2011–2014, the Swedish government ran a patient safety campaign aiming to decrease antibiotic use with the goal of yielding fewer than 250 prescriptions in outpatient care per 1000 inhabitants per year for all prescribers together (primary and secondary care, dental care) resulting in a decrease from 385 prescriptions (2011) to 328 prescriptions (2014) (Tegmark-Wisell & Cars, 2011). Finally, a national economic bonus system was introduced for regions achieving a reduction in the antibiotic prescription levels during the campaign years, and incentive for quality outcome with the same goal was introduced in 2011 at the PHCC level in the Kronoberg region.

Norway has also had a national strategy against AMR and has experienced a development similar to Sweden, with a reduction in antibiotic prescribing during the 2010s. The question is whether it is possible to reduce antibiotic use even further without harming some patients. The AMR challenge is defined as a super wicked problem where applying post-normal science analytic tools may be helpful, as traditional strategies will not be enough (Rørtveit & Simonsen, 2020).

Most physicians reduced their antibiotic prescribing over nine years

We have not found other studies examining physicians' antibiotic prescribing for RTI over time. Over nine years, the physicians were followed up at both individual and group levels. During this period, 2006-2014, the same EMR system was used in all the PHCCs in the region, including out-of-hours offices. Therefore, we believe that the dataset is comprehensive for primary care in the Kronoberg region. Since the study was performed before the development of telehealth services, the risk of missing visits via telehealth services is low, and it would not be easy to replicate the study today. To account for physicians seeing different patient groups, the antibiotic prescribing rate was adjusted for the patients' age group and sex. 78% of all antibiotic prescriptions were linked to an infection diagnosis, which is a high level compared to a study from England (Dolk *et al.*, 2018).

During the early period, there was a general reduction in antibiotic prescribing. Because we believe that the reduction was partly due to external factors, such as an enhanced vaccination programme, this could explain why most physicians reduce their antibiotic prescribing. However, Figure 11 showed that the reduction was most expressed in the Decreasing Prescribing Group, followed by the High Prescribing Group, while the Low Prescribing Group was stable.

Additionally, antibiotic stewardship was implemented through regular meetings with physicians at local PHCCs, attended by STRAMA representatives or information pharmacists. During the first years of the early period, there was also an option to subscribe to individual quarterly reports on antibiotic prescribing.

Recently, best practice guidance for antibiotic audit and feedback interventions in primary care has been published (Schwartz *et al.*, 2023).

Increasing use of point-of-care tests

We studied the use of CRP tests in patients with LRTI during the early period 2006-2014. Although not recommended in the initial judgment of LRTI, the use of CRP is known to be frequent in Scandinavia (Andre *et al.*, 2002; Läkemedelsverket & STRAMA, 2008; Larsen *et al.*, 2022; Lindstrom *et al.*, 2015). Earlier Swedish studies of CRP testing of pneumonia cases showed 38% in 2001 (Engstrom *et al.*, 2004) and 60% between 2008 and 2013 (Tyrstrup *et al.*, 2016), which is congruent with the increase that we have seen (from 61% in 2006 to 78% in 2014). From a European perspective, CRP testing is more widely used in Scandinavia compared to Continental Europe, where chest x-rays are more often used in judgment (Brown & Hay, 2024; Christensen *et al.*, 2013).

There is a debate about whether the increased use of CRP testing results in a decrease in antibiotic use. One study by van Vugt *et al.* (2013) showed that low CRP values do not exclude radiographic pneumonia, whereas a study by Lagerström *et al.* (2006) suggested that CRP testing can help exclude pneumonia. A recent Cochrane review concludes that CRP tests in RTI probably reduce the number of patients given an antibiotic prescription (Smedemark *et al.*, 2022).

The median CRP found in patients with pneumonia (62 mg/L) might be considered as low compared to, for example, the National Institute for Health and Care Excellence guidelines where CRP should be > 100 mg/L to consider pneumonia likely; however according to Swedish guidelines, pneumonia should be considered if CRP is >100 mg/L at the visit, or >50 mg/L after 1 week of duration (Folkhälsomyndigheten *et al.*, 2025; Woodhead *et al.*, 2011).

Examining the interquartiles of the CRP levels for pneumonia and acute bronchitis is interesting. The lower interquartile range for CRP in patients with pneumonia was 27 mg/L. The higher interquartile range for CRP in patients with acute bronchitis was 29 mg/L, suggesting that CRP above 30 mg/L constitutes a limit for diagnosing pneumonia, in line with the European study by van Vugt *et al.* (2013).

Doxycycline was often used in pneumonia patients with lower CRP levels in Papers II & IV. We believe this reflects that physicians suspect atypical pneumonia, such as Mycoplasma pneumonia. We need to analyse and find ways to handle this concern among physicians (Germeni *et al.*, 2018; Hedin *et al.*, 2014).

In the last ten years, the use of pulse oximetry has become a popular point-of-care test, especially during the COVID-19 pandemic. Recommendations for diagnosing pneumonia have been lacking; however, Fischer *et al.* suggest that pulse oximetry <95% and a temperature >37.8 °C should be used to suspect pneumonia (Fischer *et al.*, 2023).

CRP is just a piece of the puzzle in the total judgment of the LRTI patient.

Low use of chest x-rays and microbiological testing for the diagnosis of pneumonia

There are arguments for and against chest x-rays for pneumonia diagnosis in primary care. On the one hand, there are over- as well as underdiagnoses without x-rays imaging. On the other hand, a chest x-ray cannot determine whether the infection is bacterial or how severe it is (Wootton & Feldman, 2014).

During the early period 2008-2014, the use of chest x-rays was stable for pneumonia but increased for acute bronchitis. The overall chest x-ray rate for pneumonia was 12.4% which was higher than in a Danish study, where chest x-rays were used for 7.2% of the patients of all ages (Saust *et al.*, 2016).

Point-of-care ultrasound is not currently available in Swedish primary care, but could be helpful in the future for investigating suspected pneumonia in both children and adults and thus avoiding chest x-rays (Heuvelings *et al.*, 2019; Rodríguez-Contreras *et al.*, 2022).

We found a threefold increase in microbiological testing; however, the rate remains low. The physicians' concern about Mycoplasma and heightened awareness of AMR in general are likely to be contributory explanations for the increase.

Interpretation of diagnostic testing explains differences in antibiotic prescribing levels

In Paper III, we sought to identify any common characteristics among physicians who remained high prescribers compared to those who decreased their prescribing over time. Since we did not find earlier studies, we had to decide how to analyse the research query. We chose to focus on the RTIs since the prescribing has decreased in this group. We decided to adjust for age group and sex when calculating the antibiotic prescribing rate to account for different incidences of bacterial infections and potential missing data due to the dose-dispensing system.

Other models could have been chosen to divide the physicians into groups. However, the purpose was to have groups large enough to draw wider conclusions and groups that were relevant to compare from a clinical perspective. Additionally, one argument could be that the study is too small, with only 161 physicians from one region in Sweden with fewer than 200,000 inhabitants, and therefore cannot be generalised. However, these physicians were responsible for two-thirds of all RTI visits in the region. Furthermore, a reduction in antibiotic prescribing has been observed nationwide during the study period. Therefore, it would be reasonable to generalise to the rest of Sweden and other low-prescribing countries.

The dataset was collected before the introduction of telehealth medicine and before the onset of the COVID-19 pandemic, which may limit its relevance to current healthcare practices. However, concerning factors that influence physicians' antibiotic prescribing, we believe that this study remains relevant, as the differences between prescriber groups, the choices of point-of-care use and their interpretation, as well as the choice of diagnosis, are unlikely to be affected by telehealth services or post-pandemic healthcare.

There are some limitations. Some characteristics of the physicians were not available, such as Swedish or foreign university exams, university within Sweden, years of working experience, and form of employment. In some studies, physicians trained abroad and locum physicians have been reported as high prescribers (Borek *et al.*, 2022; Cadieux *et al.*, 2007; Silverman *et al.*, 2017; Wang *et al.*, 2009). In Paper III, most locums belong to the excluded group that had the same antibiotic prescribing rate as the included physicians.

For the patients, we have not been able to adjust for smoking, obesity, comorbidity, and socioeconomic factors.

Typically, studies of high antibiotic prescribers employ cross-sectional analyses that report differences at the group level. We argue that the physician level is more critical if we want to find areas for improvement. At the physician level, the use of the CRP test was not significantly different among the prescriber groups; however, the use of RADT for GAS was more common in the High Prescribing Group than in the other prescriber groups. Also, the High Prescribing Group used antibiotics at lower CRP levels and more often when RADT was negative.

In this study, the use of CRP testing was increasing while the antibiotic prescribing was decreasing, which is similar to paper II, where we only studied LRTI. A similar pattern was seen in a Danish study of primary care (Sydenham *et al.*, 2021). Other studies show that RADT for GAS increases antibiotic prescribing (Aabenhus *et al.*, 2017; Strandberg *et al.*, 2016; van der Velden *et al.*, 2022).

The lower median CRP levels and the higher incidence of negative RADT for GAS observed in the High Prescribing Group when antibiotics are prescribed may represent circular evidence. Assuming the patient populations are similar, this will follow if more antibiotics are prescribed. However, focusing on interpreting point-of-care results could be a way forward in antibiotic stewardship.

The most common RTI in Swedish datasets is “upper RTI” (*övre luftvägsinfektion, Öli*), which is considered to be of viral origin. Upper RTI was more often diagnosed by physicians in the Low Prescribing Group, while physicians in the High Prescribing Group were more likely to diagnose a potential bacterial infection. Several other studies have shown that the proportion of potential bacterial diagnoses corresponds to the antibiotic prescribing rate (Andre *et al.*, 2008; Hueber *et al.*, 2017; Hutchinson *et al.*, 2001). The assumption is that an infection is assigned a potential bacterial diagnosis to justify the use of antibiotics.

Seeing many patients was a risk factor for high prescribing in some studies (Akkerman *et al.*, 2005a; Cadieux *et al.*, 2007; Gjelstad *et al.*, 2011). However, McIsaac & Kukan (2023) report that high prescribers have more bacterial diagnoses. Our study also showed that the High Prescribing Group had more bacterial diagnoses, but given the lower median level of CRP, we believe that it depends on a lower threshold to identify bacterial diagnoses.

A recent Swedish study has, in two surveys, examined how physicians' views and norms affected their choices when prescribing antibiotics. Generally, physicians were more likely to use antibiotics than ordinary citizens. The physicians who choose not to prescribe antibiotics were following the perception of what most physicians would do. There was a strong correlation between private and professional attitudes. General practitioners were more likely to abstain from antibiotics than other physicians (Carlsson *et al.*, 2025).

Penicillin V was comparable to amoxicillin in the treatment of pneumonia

In Paper IV, we found no difference during the later period 2018-2021 between pneumonia cases treated with PcV and amoxicillin regarding the risk of hospitalisation for LRTI or all-cause mortality. However, pneumonia cases treated with PcV had a higher frequency of antibiotic switches than those treated with amoxicillin, doxycycline, and other antibiotics.

We found that a few patients with pneumonia (3.3%) who remained in outpatient care on day 0 were hospitalised or died on days 1-28. This indicates that the physicians' clinical evaluations and management of pneumonia patients were adequate. Other studies of patients hospitalised for CAP in the Nordic countries have shown that the most common bacterial pathogens remain *S. pneumoniae* (17-28%) and *H. influenzae* (16-31%) despite immunisation programs with the pneumococcal vaccine for children and the elderly, and *H. influenzae* type b vaccine for children (Fally *et al.*, 2021; Hansen *et al.*, 2023; Markussen *et al.*, 2024).

Treatment with amoxicillin compared to PcV was not different in proportion of hospitalisation for LRTI or all-cause mortality, but resulted in fewer antibiotic switches. At paediatric clinics, children <5 years with pneumonia had a lower risk of antibiotic switch or pneumonia-associated hospitalisation, but the same risk of severe complications when treated with amoxicillin compared to PcV (Rhedin *et al.*, 2024). Hospitalised adults with non-severe CAP showed no difference in 30-day mortality between penicillin G/V and broad-spectrum antibiotics (Rhedin *et al.*, 2017). In Paper IV, the 28-day mortality rate was low but higher for amoxicillin compared to PcV (1.6% and 0.42% of pneumonia cases, respectively). One reason for the higher mortality rate could be that amoxicillin is generally considered to be a better treatment choice than PcV for severe pneumonia.

A Norwegian study (Blandhol *et al.*, 2017) showed that antibiotic switches within ten days were more common after a PcV prescription (4.2%) than other RTI antibiotics (<2.6%), similar to Paper IV. Aside from assuming lower bioavailability and lower efficacy of PcV, one possible explanation for why antibiotic switches were more frequent within the PcV group could be that physicians are more prone to switch antibiotics if the initial treatment is narrow-spectrum.

No excess antibiotic prescribing during out-of-hours

In Paper I, we examined infection visits and the use of antibiotics at OOHCs during the early period (2006-2014). Over time, the number of OOH infection visits decreased by a third. Factors contributing to the decrease included shorter opening hours at the end of the study, a penalty fee (€ 100) introduced in 2008 for the PHCC for each patient attending the OOHC, and the introduction of a nurse triage system for walk-in patients.

The OOH antibiotic prescription rate per 1000 inhabitants per year was at the same level in the Netherlands, Sweden, and England (with 20, 28, and 31 prescriptions, respectively), but higher in Denmark (80 prescriptions) (Debets *et al.*, 2017; Hayward *et al.*, 2016; Huibers *et al.*, 2014). Two English studies have shown stable or increased OOH antibiotic prescription rates from 2010 to 2014 (Edelstein *et al.*, 2017; Hayward *et al.*, 2016). In contrast, Paper I showed a decrease in antibiotic prescription rates.

We found that the relative risk of antibiotic prescribing during OOH decreased when adjusting for diagnosis, as acute media otitis, pharyngotonsillitis, and lower UTIs, which often require antibiotics, were more common during OOH than during IH. Apart from the high relative risk of receiving antibiotics for skin and soft tissue infections during OOH, there are no apparent areas to intervene.

This is in contrast to a literature review of qualitative and quantitative studies of antibiotic prescribing during OOH, where overprescribing to self-limiting conditions, prescribing of broad-spectrum antibiotics, time constraints, safeguarding issues, and poor communication contributed to inappropriate prescribing (Hart & Phillips, 2020). Alves *et al.* (2021) found no guidelines addressing the challenges of antibiotic prescribing during OOH. They suggested that OOH-focused resources need to be developed, given the high antibiotic prescribing rate. We believe that OOH-focused resources are not needed, but rather general antibiotic stewardship.

No excess prescribing of broad-spectrum antibiotics during out-of-hours

In Paper I, we also found that the relative use of different antibiotics for the six most common diagnoses during the early period (2006-2014) was comparable between IH and OOH. The relative use of narrow-spectrum antibiotics was higher during OOH. A possible explanation could be that primary infection visits were more common during OOH.

The result corresponds with other quantitative studies from Norway and the Netherlands (Debets *et al.*, 2017; Fagan, 2008) and with a qualitative Belgian study where physicians reported the treatment choice to be the same as during IH, although the threshold to prescribe was lower at OOHCs (Colliers *et al.*, 2018). In contrast, an English study noted a higher proportion of broad-spectrum antibiotics during OOH (Edelstein *et al.*, 2017).

Fewer antibiotics in acute bronchitis

In Paper II, we found that the antibiotic prescription rate of acute bronchitis decreased from 74% in 2006 to 41% in 2014. The decrease continued during the later period, with 33% in 2019 and even lower during the pandemic. Still the rate is high since guidelines recommend no antibiotic treatment at all (Läkemedelsverket & STRAMA, 2008). In comparison, the prescription rate for acute bronchitis in the US appears to be increasing, while the rate in Denmark is significantly lower (Barnett & Linder, 2014; Saust *et al.*, 2016). Intervention in the US has only given a modest result (Ackerman *et al.*, 2013). The Happy Audit intervention resulted in a reduction of antibiotics in LRTI with more than 25% in some countries (Bjerrum *et al.*, 2011).

As mentioned before, physicians are often supposed to decide on the treatment first and then make the diagnosis. If that were true, we would expect to see an increase in pneumonia cases when the number of acute bronchitis cases treated with antibiotics decreases, but that is not the case. Also, the decrease could not be attributed to the fewer infections due to the vaccination programmes.

In this case, it is more likely that the prescription pattern has been influenced by STRAMA's efforts to increase awareness of the potential risks of antibiotic resistance. It may also have raised awareness and contributed to increased knowledge in the general population (Molstad *et al.*, 2008; Molstad *et al.*, 2017). It could explain why we see different patterns in different countries.

The antibiotic prescription rate for acute bronchitis is decreasing, while the CRP testing is increasing. CRP is likely used to aid in the diagnosis of acute bronchitis and to help inform decisions about antibiotic use. However, it may also reflect the absence of clear diagnostic criteria for pneumonia and a perceived need for diagnostic tests in primary care settings (Bisgaard *et al.*, 2021).

Nine out of ten low prescribers remained low prescribers

An interesting finding in paper III was that low antibiotic prescribers remained low prescribers over time. At a PHCC in the Kronoberg region in the 1990s, it was found that the antibiotic prescribing rate between the five physicians differed from 25% to 72%. There was an intervention where the antibiotic prescribing was discussed within the physician group, and a handful of principles were agreed upon. In the following years, the antibiotic prescribing rate remained unchanged. Low prescribers remained low, and high prescribers remained high (Cars & Hakansson, 1995).

The only significant characteristic of the Low Prescribing Group was that they were more likely to have few RTI visits. The reason is unclear. Apart from being attributed to random chance, the physicians of the Low Prescribing Group may be more experienced or have more chronic patients.

In contrast to other studies (Akkerman *et al.*, 2005b; Baillie *et al.*, 2024; Hueber *et al.*, 2017; Miyawaki *et al.*, 2025; Silverman *et al.*, 2017; Tell *et al.*, 2015; Wang *et al.*, 2009) from Sweden and abroad, we found that the antibiotic prescribing rate was not affected by the physicians' age, and we did not see an increase in antibiotic prescribing over time, which would have been expected in the nine-year-long study. Rather, the higher prescribing rate seen among older physicians in other studies probably reflects a higher general prescribing rate when the physicians were younger.

Seeing a low-prescribing physician did not result in more return visits or secondary antibiotic prescriptions

In Paper III, we also studied the risk of return visits or antibiotic switches within a month, depending on which physician the patient had met. The return visit rate was lower (14%) compared to earlier studies, where rates ranging from 27% to 38% have been reported. Some of these studies have reported a higher return visit rate if antibiotics were prescribed at the index visit, and others have shown the opposite (Cals *et al.*, 2009; Holmes *et al.*, 1997; Little *et al.*, 1997). The low return visit rate in Paper III was probably due to generally fewer consultations per inhabitant in Sweden. We found a slight difference in return visit rate amongst the prescriber groups, but the difference was clinically irrelevant. At the physician level, the only difference was a lower return visit rate in the Decreasing Prescribing Group compared to the High Prescribing Group. No difference was seen in the proportion of a second antibiotic prescription within a month. This indicates that the Low Prescribing Group was still not prescribing too few antibiotics.

General reduction of respiratory tract infections during the COVID-19 pandemic

The SSD database includes the first two years of the COVID-19 pandemic and showed a reduction to less than half in the incidence of pneumonia. The decreased incidence of pneumonia during the COVID-19 pandemic is intriguing. Many reasons could account for this. For instance, apart from the SARS-CoV-2 virus, fewer microbes were probably circulating. In Sweden, the following recommendations were promoted: social distancing, hand washing, working from home whenever possible, avoiding non-essential travel, and staying home when sick. However, school closures and the use of face masks were promoted to a lesser extent compared to other countries (Ludvigsson, 2023). The threshold for seeking healthcare was higher.

A similar pattern with a halving of the number of RTI visits was seen in several other countries on different continents, except Norway where no decrease was seen (Westfall *et al.*, 2024).

In Paper IV, there were only minor changes in antibiotic treatment choice and hospitalisation rates during the COVID-19 pandemic. Simply, fewer patients were infected, and the management was unchanged.

(F)actors

To summarise the discussion, I have looked at how the results affect the (f)actors mentioned in the background.

The disease

During the years of our studies, we have seen diseases come and go. In 2008, we had the new influenza (H1N1, swine influenza) that, in the end, did not affect primary care. In 2011, there was an increase in Mycoplasma diagnoses. We have had a fusidic acid-resistant Staphylococcus strain.

Finally, in 2020, the COVID-19 pandemic emerged, transforming the primary care system in numerous ways. During the COVID-19 pandemic, the number of infections decreased to less than half the earlier incidence. This shows that the constraints against COVID-19, such as limited contacts, social distancing, and better hand hygiene, also affected other infections, although the lockdown was less severe in Sweden compared to other countries (Ludvigsson, 2023).

The patient

As stated in the introduction, the patient is a crucial factor. In Papers I, III & IV, we have adjusted the data for age group and sex. The advantage is that the data is comparable. The disadvantage is that the patient factor becomes hidden.

In qualitative studies, physicians often claim that they prescribe antibiotics in some cases due to the patient's wish (O'Connor *et al.*, 2018). One systematic review found that physicians' perception of patients' desire for antibiotics, as opposed to patients' actual desire, was associated with antibiotic prescribing (McKay *et al.*, 2016). These aspects are difficult to study in the datasets of this thesis. A possibility would have been to conduct a multilevel analysis to determine if there is an association at the patient level between earlier antibiotic prescription and the risk of a new prescription at the next infection episode.

The physician

Since the physician evaluates the patient's symptoms and, if needed, prescribes antibiotics, the physician's role is essential. I have already demonstrated that there is a large unexplained variability between the physicians.

Most physicians have reduced their antibiotic prescribing in line with the general reduction. Still, there is a large variability in the antibiotic prescribing rate, which indicates that there could be inappropriate antibiotic prescribing. We found that the inappropriate prescribing was less than expected in OOHCs. Also, we found that physicians in the High Prescribing Group were more likely to identify a bacterial diagnosis, and seeing a physician belonging to the Low Prescribing Group does not lead to more return visits or antibiotic switches, indicating that their prescribing level is not too low.

From an international perspective, the focus is on inappropriate antibiotic prescribing, and studies have been conducted to quantify the level (Schwartz *et al.*, 2020) and to identify interventions to reduce inappropriate prescribing. In a systematic review from 2018, the following interventions were identified as effective: parent education, combined patient/clinician education, procalcitonin testing for adults with LRTIs, and electronic decision support systems (McDonagh *et al.*, 2018). Later studies have suggested interventions such as audit and feedback, and participatory action research (Colliers *et al.*, 2023; Saqib *et al.*, 2025).

Generally, the reductions following the interventions were limited. The variability among countries is much broader than the results of the interventions. Since there do not seem to be any problems with low-prescribing physicians in a low-prescribing country like Sweden, we believe that there is room for improvement in many countries.

The nurse

Since a large part of the visits in primary care pass through nurse triage, we believe that the nurses' role in the management of infections is important, but often overlooked. One major problem in assessing the nurses' impact is that their activity is documented in different ways. They may write a whole record, including diagnosis codes, in the EMR, a short note or nothing at all. My goal was to analyse their role, but it has been postponed to a later stage. As the organisation is changing with more telehealth medicine, the nurses' role will also change.

The antibiotic

In Paper IV, we have shown that penicillin V, the traditional treatment of pneumonia in primary care, was equivalent to amoxicillin in avoiding hospitalisation for LRTI or all-cause mortality.

Traditionally, the antibiotic courses are prescribed for a fixed duration, but it is said that many patients stop taking the antibiotics when they feel better. Llor asks in a letter if perhaps the patient should decide how many days to take the medication (Llor, 2025). An audit reports the duration of antibiotics to be longer than the guidelines prescribe and recommends shorter courses to minimise unnecessary exposure (Llor *et al.*, 2025).

The organisation

As we have seen, there has been a decrease in RTIs and antibiotic use among children. It is likely that the decline, to a large part, depends on external factors. A similar reduction has been observed in other countries. Therefore, we believe that it is a result of the expanded vaccination program for children with the introduction in 2009 of the pneumococcal conjugate vaccine, where a lower rate of both common acute otitis media and severe infections in young children has been observed (Alfven *et al.*, 2024; Johansson Kostenniemi *et al.*, 2018). If the decrease had been a result of antibiotic stewardship, we would have seen an effect on the adult population as well.

Another explanation for the decreasing number of infection visits could be due to the lack of primary care physicians. During the 2010s, many physicians retired, and the number of unfilled positions rose. Also, it is possible that the nurses would handle more infection visits.

During the early period, telehealth medicine was not available. During the later period, especially young adults choose telehealth consultations (Ekman *et al.*, 2019). In this thesis, we have not analysed the consequences of the increased use of telehealth medicine.

Before 2012, the prescriptions to older patients using dose-dispensed medication were written by hand and faxed to the pharmacy. Those prescriptions were rarely documented in the EMR. Today, more antibiotic prescriptions are reported in the pharmacy database of dose-dispensed medication. However, patients living in nursing homes often get antibiotics from local storages, and these prescriptions will not be recorded as collected from the pharmacy.

The guidelines

The guidelines make an impact. The guidelines for UTI in men have switched from recommending ciprofloxacin to narrow-spectrum antibiotics, resulting in a lower use of ciprofloxacin without increasing complications in both Sweden and Norway (Kornfalt Isberg *et al.*, 2020; Saetre *et al.*, 2024).

In Paper I, 83% of patients with sinusitis received antibiotics during the early period, which is comparable to other Swedish studies (Cars *et al.*, 2017; Tyrstrup *et al.*, 2017). With the introduction of nasal steroids and updated guidelines, the antibiotic prescription rate for sinusitis has decreased to 50% in the Kronoberg region during the later period (unpublished data, the SSD database), but there is still room for improvement.

Generally, switching to do something else is easier than switching to do nothing. In Paper III, we see many antibiotic prescriptions for pharyngotonsillitis, although the RADT is negative (Table 4).

Soft variables

To understand why physicians prescribe antibiotics outside the guidelines, soft variables – special circumstances – are gaining more attention. Examples of soft variables are diagnostic uncertainty, patients' expectations, sympathy with the patient, cultural norms at the PHCC and in the society, and danger of delayed treatment (Andre *et al.*, 2016; Bisgaard *et al.*, 2021; Hueber *et al.*, 2017; O'Connor *et al.*, 2018; Petursson, 2005; Szymczak *et al.*, 2024; Thaulow *et al.*, 2023).

We found it difficult to track soft variables in these datasets, but one suspicion is that physicians in the High Prescribing Group were more likely to identify soft variables. A qualitative study focusing on the physicians' sensitivity to react to soft variables could be valuable.

Variability

As shown in Figure 20, the variability was at the same level during the later period as during 2010-2012, although the antibiotic prescription rate was lower.

An Australian study showed that early-career physicians had a substantial inter-practice variation in antibiotic prescribing for acute RTI and particularly for acute bronchitis, where the antibiotic prescribing rate ranged from 0% to 100%. The authors suggested that the practice environment or culture may influence the prescribing habits (Turner *et al.*, 2025). We have seen a preliminary correlation between junior and senior physicians at the PHCC level (unpublished data, the KIDPC database), which may warrant further examination.

Implication

Are we at the end of the road?

The use of antibiotics has declined for decades, but could it continue? Considering the goal of reducing antibiotic use to combat AMR, it is a crucial question. The reduction has been observed primarily in RTI and among children. Even though we would like to think that it is a result of antibiotic stewardship by STRAMA, it is more likely to be a result of the expanded vaccination programme for children. The development has been similar in other countries in parallel with an expanded vaccination programme.

PcV remains the first-line treatment for pneumonia

Is narrow-spectrum PcV effective enough in a clinical context? In patients with pneumonia, antibiotic switches were more common with PcV than with other antibiotics. However, treatment with PcV posed the same risk for hospitalisation for LRTI or all-cause mortality as amoxicillin did. The current Swedish guidelines that recommend PcV as a first-line treatment can remain. Other countries with resistance patterns similar to Sweden's may consider adding PcV to their guidelines. Still, as the future aetiology of pneumonia is unknown, surveillance of the aetiology in primary care would be essential in the future.

Physicians can decrease their antibiotic prescribing

In Paper III, we found that over nine years, most physicians decrease their prescribing. The prevalence and the antibiotic prescribing rate of acute bronchitis have decreased. These changes are likely to be a result of antibiotic stewardship. Further decrease is possible if we achieve less variation on a low prescribing level.

Promote not using point-of-care tests without an indication

Paper III demonstrated that high-prescribers tended to overuse point-of-care tests, and that the quality of test interpretation could be improved. Antibiotic stewardship can continue to focus on providing continuous medical education on indications, usefulness, and interpretation of point-of-care tests. Correct diagnosis is crucial for maintaining high-quality antibiotic prescribing.

Interventions focused on out-of-hours centres are not necessary

Although the antibiotic prescribing rate was higher during OOH than during IH, when adjusted for diagnoses, the difference was so minimal that interventions focused on OOHCs are not necessary.

Further reduction of antibiotic prescribing is possible

In view of the fact that patients who see low-prescribing physicians do not have more return visits or antibiotic switches than patients who see high-prescribing physicians, we believe that there is still room for further reduction, at least among high-prescribing physicians. The result could be helpful for further development of antibiotic stewardship in the STRAMA organisation and for implementation at local, regional and national levels.

Future antibiotic stewardship

The studies to date provide valuable information for future antibiotic stewardship. There is no need for antibiotic stewardship targeting out-of-hours. It is not possible to easily identify one group of prescribers that would gain more from antibiotic stewardship promotion. Interventions targeting a chain of behaviour could be a potential road forward. This will be explored in future studies.

Guideline update

When the guidelines are updated, the implications from the papers and the thesis may be taken into account.

Conclusion

Sweden is one of the countries with the lowest antibiotic use in Europe. For three decades, there has been a decline in antibiotic prescribing due to both external factors, such as expanded vaccination programmes and internal factors, including antibiotic stewardship by STRAMA.

Since over-prescribing at out-of-hours centres is limited when adjusted for diagnoses, it is unlikely that interventions towards out-of-hours centres will be effective. Parallel with the increase of point-of-care tests, the diagnosis of acute bronchitis and antibiotic prescribing have decreased.

Most physicians have reduced the antibiotic prescription rate over time. Few physicians have increased their prescribing. High prescribers are more likely to identify a bacterial diagnosis and treat with antibiotics, even in cases with low levels of CRP or negative RADTs. Low prescribers have the same rate of return visits or treatment failures as high prescribers. Interventions may be focused on behaviour.

Studying the management of pneumonia closely and gaining a better understanding of how the diagnosis is investigated and why certain treatments are used could provide important information when it is time to revise the pneumonia guidelines in primary care.

My research idea was to understand the reasons for the variability of antibiotic prescribing. I encountered challenges that made it difficult to capture data and analyse my research idea. Furthermore, when I met reality, I had to adjust my study plans and do research that is funded. The result is that the content of my research has changed over the years, and so has this thesis. Real-world data can be used to measure variability, but it remains challenging to understand the underlying reasons behind the variability. To get further qualitative dialogues with prescribers will be essential to be able to afford more in-depth analyses.

Even though I did not reach the goal of explaining the variability, I have found answers to some of the questions which are presented in this thesis. In conclusion, I hope these studies can contribute to some pieces of evidence to the big puzzle of the management of infections and antibiotic prescribing in primary care.

Future thoughts

There are several directions for future research to understand the variability. One ambition not achieved within the frame of this thesis is to conduct a qualitative study of focus group discussions with both physicians and nurses concerning the possibilities and hurdles to follow the guidelines of the management of LRTI. Another qualitative topic would be to learn about physicians' beliefs and thoughts concerning soft variables as compassionate reasons for antibiotic prescribing.

Other more quantitative approaches are the treatment of children with pneumonia and the treatment of pneumonia in elderly care. The position of doxycycline needs to be analysed through studies that include information about disease severity and duration.

The use of modern tools such as oxygen saturation measurement and point-of-care ultrasound would also be interesting to evaluate. Also, the position of vital parameter scans that are being introduced, as well as personal health gadgets that measure pulse, saturation, breathing frequency and more, need to be examined.

At the organisational level, we have seen the impact of telehealth services and also changes in offers from pharmacies.

Finally, there is the use of AI in infections in primary care. On the one hand, there are immense possibilities, and on the other hand, there are challenges such as ethical aspects. In research methodology, let AI find asymmetries in the dataset to identify errors.

To further research in this area, I believe it is important to keep the everyday aspect of seeing patients with infections so that interventions of the management of infections and antibiotic prescribing are feasible in a primary care setting.

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Paper I

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RESEARCH ARTICLE Open Access

Diagnosis-linked antibiotic prescribing in Swedish primary care - a comparison between in-hours and out-of-hours

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Abstract

Background: The rise in antibiotic resistance is a global public health concern, and antibiotic overuse needs to be reduced. Earlier studies of out-of-hours care have indicated that antibiotic prescribing is less appropriate than that of in-hours care. However, no study has compared the out-of-hours treatment of infections to in-hours treatment within the same population.

Methods: This retrospective, descriptive study was based on data retrieved from the Kronoberg Infection Database in Primary Care (KIDPC), which consists of all visits to primary care with an infection diagnosis or prescription of antibiotics during 2006–2014. The purpose was to study the trends in antibiotic prescribing and to compare consultations and prescriptions between in-hours and out-of-hours.

Results: The visit rate for all infections was 434 visits per 1000 inhabitants per year. The visit rate was stable during the study period, but the antibiotic prescribing rate decreased from 266 prescriptions per 1000 inhabitants in 2006 to 194 prescriptions in 2014 (mean annual change − 8.5 [95% CI − 11.9 to − 5.2]). For the out-of-hours visits (12% of the total visits), a similar reduction in antibiotic prescribing was seen. The decrease was most apparent among children and in respiratory tract infections.
When antibiotic prescribing during out-of-hours was compared to in-hours, the unadjusted relative risk of antibiotic prescribing was 1.37 (95% CI 1.36 to 1.38), but when adjusted for age, sex, and diagnosis, the relative risk of antibiotic prescribing was 1.09 (95% CI 1.08 to 1.10). The reduction after adjustment was largely explained by a higher visit rate during out-of-hours for infections requiring antibiotics (acute otitis media, pharyngotonsillitis, and lower urinary tract infection). The choices of antibiotics used for common diagnoses were similar.

Conclusions: Although the infection visit rate was unchanged over the study period, there was a significant reduction in antibiotic prescribing, especially to children and for respiratory tract infections. The higher antibiotic prescribing rate during out-of-hours was small when adjusted for age, sex, and diagnosis. No excess prescription of broad-spectrum antibiotics was seen. Therefore, interventions selectively aiming at out-of-hours centres seem to be unmotivated in a low-prescribing context.

Keywords: Antibiotic prescribing, Diagnosis-linked prescription, Electronic health records, Infectious disease, In-hours, Out-of-hours service, Primary care

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Background

The rise of antibiotic resistance is a global public health threat according to the World Health Organization [1], and antibiotic overuse is common and results in medicalization, unnecessary costs, and increased antibiotic resistance [2]. However, studies on antibiotic prescribing in primary care regardless of indication show a high level of variability between physicians in different countries [3–5].

In primary care in-hours (IH) are usually office hours (in Sweden 08:00 to 17:00) during business days, and out-of-hours (OOH) are the remaining hours. Earlier studies of OOH care have suggested that compared to IH care there are lower adherence to antibiotic guidelines [6, 7], a higher antibiotic prescribing rate [8, 9], a higher rate of prescriptions for broad-spectrum antibiotics [8], and more antibiotic prescriptions during weekends than weekday evenings [10]. In a qualitative study from Belgium, the physicians reported that the threshold for prescribing antibiotics was lower during OOH, but the choice of antibiotics was the same [11]. A more recent Belgian OOH study showed a high antibiotic prescribing rate for all indications, a high rate of not using recommended antibiotics, and an overuse of quinolones [12]. However, a Dutch study found the prescribing quality to be appropriate, and the higher rates of prescribing in OOH were explained by a different population of presenting patients [13]. No previous study has compared the OOH treatment of infections to IH within the same population.

Although Sweden belongs to the European countries with low levels of antibiotic prescriptions, there is still room for improvement [14]. Previous registry-based studies in Sweden have shown a significant reduction in antibiotic prescriptions over the last decade, but these studies have not included OOH [15–17]. Several Swedish national guidelines concerning the evaluation and treatment of infectious diseases have been published [18–22], and generally these guidelines aim at better diagnostics, fewer antibiotics, and more targeted treatments.

Because visits for infectious diseases are common at OOH centres, it is important to evaluate whether OOH visits are associated with increased antibiotic prescribing rates because this would warrant interventions in OOH settings.

The purpose of the study was to describe the trends in antibiotic prescribing over time and to compare diagnosis-linked prescribing in general and in detail between IH and OOH in the same population.

Methods

Description of the study population

In 2014, Kronoberg County in southern Sweden had 189,128 inhabitants, which was equal to 2% of the Swedish population [23]. During 2014, there were a total of 243,502 physician visits for all causes and 238,164 other visits (nurses, physiotherapists, behavioural therapists) in primary care, thus there were 1300 physician visits and 1300 other visits per 1000 inhabitants.

During the study period, the number of primary healthcare centres (PHCCs) varied between 28 and 35, with 1–8 family physicians each. There were approximately 100 family physician positions and 50 junior physician positions. At the study start, all PHCCs were publicly run, but since March 2009 a third of the PHCCs have been privately run due to new legislation allowing publicly funded private PHCCs.

At the PHCCs, the patient normally booked an appointment through a telephone call with an office nurse who assessed if the patient needed a physician visit. IH were business days 08:00 to 17:00. In the region there were two OOH centres (OOHCs), and the PHCCs staffed the OOHCs with physicians. Patients were supposed to call a nurse triage first, but could also walk in. The visit fees were the same as for IH visits. Home visits were rare, and usually only performed for urgent cases at elderly care homes. Nurses at the OOHCs were responsible for phone advice, and there was also a national phone advice number for patients where nurses provided medical advice. At the time of the study, no Internet services were available.

OOHC 1 served approximately 125,000 inhabitants and was situated in the neighbourhood of the hospital in city 1. During 2006–2007 the centre was open from 17:00 to 24:00 on weekdays and from 08:00 to 24:00 on weekends and holidays. From 2008 the centre closed at 21:00. Walk-in patients met a nurse who assessed whether a meeting with a physician was warranted.

OOHC 2 served approximately 63,000 inhabitants and was situated at the emergency department of the hospital in city 2. During 2006–2007 the centre was open from 17:00 to 08:00 on weekdays and around the clock on weekends and holidays. From 2008 the centre closed at 21:00. Walk-in patients generally got to see a physician.

The Kronoberg infection database in primary care (KIDPC)

This retrospective, descriptive study was based on data from the KIDPC database, which contains information on all visits with an infection diagnosis and all antibiotic prescriptions with or without a visit in primary care in Kronoberg County in 2006–2014. Annually, there were on average 86,000 visits for infections and 43,000 antibiotic prescriptions reported in the database.

The data in the KIDPC were extracted from the electronic medical records (EMR) used in Kronoberg County (Cambio Cosmic software, Cambio Healthcare Systems AB, Linköping, Sweden) at one instance in 2015 using

BusinessObjects (SAP AG, Walldorf, Germany). These data contain detailed information about the patients (age, sex, anonymous ID), the visits (PHCC, geography, IH or OOH), the care providers (physicians, nurses), the investigations (diagnostic tests, x-rays, cultures), and the prescriptions (drugs, dosages, durations). The data were linked together using the anonymous patient ID and visit date. For all physician visits, at least one diagnosis was registered according to the simplified Swedish primary care edition of the *International Classification of Disease and Related Health Problems – Tenth Revision* (ICD-10) [24]. The diagnoses were validated and grouped into four main groups and several subgroups by one of the authors (OC) according to recommendations by Public Health Agency of Sweden [25]. The main groups are respiratory tract infections (RTIs), urinary tract infections (UTIs), skin and soft tissue infections (SSIs), and other infections. The RTI group includes ear infections, and the UTI group includes urogenital infections. The other infections group includes eye infections, gastrointestinal infections, and rare infections (See Additional file 1). Because at least one diagnosis had to be recorded for each physician visit, the data set is considered to be complete. However, no diagnoses were recorded for phone, mail or e-mail consultations, and in these cases, the prescriptions could not be linked to a diagnosis.

Antibiotic prescriptions were identified according to Anatomical Therapeutic Chemical Classification (ATC) code group J01, which includes all oral and parenteral antibiotics, but not antibiotics in ointments or eye drops. Antibiotic prescriptions were linked to diagnoses if within a week after a visit. Antibiotic treatment without a diagnosis of an infection could also result from consultation with a care provider other than a physician or from a non-infection diagnosis at a visit. Information on whether the patients collected the medication at the pharmacies was not available in the present study.

Data set

All physician visits with an infection diagnosis and all antibiotic prescriptions were extracted from the KIDPC database, resulting in a data set with 702,048 physician visits and 389,263 prescriptions over 9 years. For each visit, data on the patient's age and sex, infection diagnoses, antibiotic treatments, and PHCC were extracted.

A visit was defined as a physical visit to a physician, and a consultation was defined as a phone, mail, e-mail or nurse contact. It was compulsory for the physician to code the diagnosis when documenting the visit. Only physician coded diagnoses were used in this study for consistency. In 3% of the visits more than one infection diagnosis was recorded, and in these cases the main diagnosis was selected based on the severity and the likelihood of the diagnosis resulting in an antibiotic prescription. Consultations were not coded for diagnoses, but could in some instances result in antibiotic prescriptions, for example treatment for UTI or repeat prescriptions.

This study presents descriptive annual data and mean annual change for infections and antibiotic prescribing per 1000 inhabitants divided per main infection group, age group, sex, and per IH and OOH (Tables 1, 2, 3, 4). The data are presented as numbers per 1000 inhabitants per year based on the population of the region as of December 31 of each year. Because the population of Kronoberg County is only 2% of the population of Sweden and the antibiotic prescription rate was lower than the average in Sweden [26], the numbers reported cannot be extrapolated to the national level. However, the trends are likely to be generalisable.

The IH and the OOH cohorts were compared. The relative risk of receiving antibiotics during OOH was calculated (Table 5). The proportions of the choice of antibiotics for common infections were reported (Table 6).

Statistical methods

All analyses were performed using Excel 2013 (Microsoft, Redmond, WA, USA) and SPSS Version 23 (IBM Corp, Armonk, NY, USA). For descriptive statistics, means, and proportions were used. For annual trends, linear regressions were calculated and presented as mean annual change with 95% confidence interval. Comparisons between groups after adjusting for sex, age, and diagnosis were presented as relative risks with 95% confidence interval. Comparisons between proportions of categorical variables in two independent groups were performed with the chi-square test. P-values ≤ .05 were considered statistically significant.

Results

The physician visit rate for infections varied during the study and reached a maximum of 469 visits per 1000 inhabitants per year in 2011 and a minimum of 398 visits in 2014. Female patients have more infection visits than male patients, 502 and 366 visits per 1000 inhabitants per year respectively. Children 0–4 years and adults over 80 years had the highest visit rates, 995 and 576 visits per 1000 inhabitants per year respectively. No significant trends were observed in total visit rate nor in visit rate by sex, but the mean annual change in visit rate per 1000 inhabitants per year decreased in children 0–4 years (− 33.7 (95% CI − 56.0 to − 11.5)), increased in adults 65–79 years (7.7 (95% CI 1.1 to 14.3) and in adults over 80 years (13.9 (95% CI 7.6 to 20.2)) (Tables 1 and 2).

Table 1 Visits according to the type of infection per 1000 inhabitants per year

	Visits per 1000 inhabitants and year										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	Average 2006–2014	Mean annual change (95% CI)
All hours											
Respiratory tract infections[a]	241	258	243	253	255	267	258	234	205	246	− 2.9 (−8.3 to 2.5)
Skin & soft tissue infections	58	59	60	68	67	72	71	71	69	66	1.7 (0.8 to 2.6)
Urinary tract infections	51	52	51	54	55	54	52	51	49	52	−0.2 (−0.7 to 0.4)
Other infections[b]	61	60	61	69	71	76	77	74	75	69	2.2 (1.3 to 3.2)
Total all hours	412	430	416	445	448	469	457	430	398	434	0.9 (−6.5 to 8.3)
In-hours											
Respiratory tract infections[a]	200	215	207	223	227	238	230	209	182	215	−0.5 (−6.1 to 5.1)
Skin & soft tissue infections	51	52	54	62	62	67	65	65	63	60	1.8 (0.8 to 2.9)
Urinary tract infections	42	43	43	47	48	47	44	45	42	45	0.1 (−0.6 to 0.8)
Other infections[b]	53	53	55	64	66	70	71	68	69	63	2.5 (1.4 to 3.5)
Total in-hours	347	364	360	397	402	421	410	387	356	382	3.9 (−4.1 to 11.9)
Out-of-hours											
Respiratory tract infections[a]	42	42	36	30	28	30	28	25	23	32	−2.3 (−3.1 to − 1.6)
Skin & soft tissue infections	6.9	7.1	6.0	5.5	5.5	5.9	5.5	5.7	6.4	6.1	−0.1 (−0.3 to 0.1)
Urinary tract infections	9.0	8.9	8.0	7.0	7.3	7.0	7.5	6.6	7.1	7.6	−0.3 (−0.4 to − 0.1)
Other infections[b]	7.7	7.5	6.0	5.4	5.5	5.8	5.7	5.7	5.7	6.1	−0.2 (−0.4 to 0.0)
Total out-of-hours	65	66	56	48	46	48	47	43	43	51	−3.0 (−4.2 to −1.7)

[a] Includes ear infections
[b] Includes eye infections, gastrointestinal infections, and rare infections

The antibiotic prescriptions per 1000 inhabitants per year decreased significantly from 266 prescriptions in 2006 to 194 prescriptions in 2014 (mean annual change − 8.5 (95% CI − 11.9 to − 5.2)). There was no sex difference, but the decrease in antibiotic prescriptions was more pronounced in children 0–4 years (mean annual change − 35.2 (95% CI − 46.9 to − 23.5)) and in children 5–19 years (mean annual change − 11.7 (95% CI − 17.0 to − 6.5). The antibiotic prescribing frequency decreased mainly for RTIs (mean annual change − 6.5 (95% CI − 9.0 to − 3.9)), explaining 76% of the total reduction. Antibiotic prescriptions without an infection diagnosis and prescriptions for UTIs also decreased, explaining a further 11 and 8% of the total reduction, respectively (Tables 3 and 4).

Of all antibiotic prescriptions, 75% were linked to an infection visit on the same day, another 3% were linked to an infection visit within a week before the prescription day, and finally 22% were not possible to link to an infection visit. These proportions were stable during the study period. Of all antibiotics prescribed at visits, 66% were antibiotics commonly used for RTIs, 12% were commonly used for SSIs, 16% were commonly used for UTIs, and 6% were other antibiotics. Of the antibiotics prescribed without an infection diagnosis, 38% were antibiotics commonly used for RTIs, 25% were commonly used for SSIs, 29% were commonly used for UTIs, and 8% were other antibiotics. Of the UTI antibiotics, 36% were prescribed without an infection diagnosis.

During the study period, the OOH infection visits decreased from 65 visits per 1000 inhabitants in 2006 to 43 visits in 2014 (mean annual change − 3.0 visits (95% CI − 4.2 to − 1.7)). Also, the antibiotic prescribing decreased from 43 prescriptions per 1000 inhabitants in 2006 to 26 prescriptions in 2014 (mean annual change − 2.2 prescriptions (95% CI − 3.3 to − 1.2)).

The diagnoses and antibiotic prescription rates between IH and OOH are shown in Table 5. During IH, there were 382 infection visits per 1000 inhabitants per year compared to 51.4 during OOH. Thus 12% of all visits were during OOH. RTIs were the most common diagnoses during both IH and OOH. However, acute otitis media, pharyngotonsillitis, and lower UTIs were more common during OOH. A total of 15% of all antibiotics were prescribed during OOH. The likelihood of receiving an antibiotic prescription was 55% during OOH visits compared to 41% during IH visits. The unadjusted relative risk of antibiotic prescribing in OOH was 1.37 (95% CI 1.36 to 1.38) compared to IH. The difference remained unchanged when only adjusted for age and sex 1.37 (95% CI 1.37 to 1.38) and 1.37 (95% CI 1.37 to 1.38), respectively. However, when adjusted for age, sex,

Table 2 Visits due to infections according to sex and age group per 1000 inhabitants per year

	Visits per 1000 inhabitants per year										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	Average 2006–2014	Mean annual change (95% CI)
All hours											
Female	477	499	481	514	517	546	528	500	458	502	0.9 (−8.0 to 9.8)
Male	345	369	351	376	380	393	386	362	336	366	0.5 (−5.9 to 6.8)
Age (years)											
0–4	997	1172	1062	1059	1079	962	958	867	796	995	−33.7 (−56.0 to − 11.5)
5–19	494	498	451	481	492	511	468	433	382	468	−9.7 (− 19.6 to 0.3)
20–39	376	383	353	381	377	406	393	357	331	373	−2.5 (− 9.5 to 4.5)
40–64	319	329	315	348	349	379	368	356	326	343	4.1 (−2.2 to 10.4)
65–79	404	407	396	432	428	471	474	460	431	434	7.7 (1.1 to 14.3)
≥ 80	506	522	552	570	578	610	632	616	595	576	13.9 (7.6 to 20.2)
In-hours											
Female	403	425	418	460	464	492	475	451	410	444	4.2 (−5.3 to 13.7)
Male	288	311	303	334	340	351	346	324	299	322	3.1 (−3.7 to 9.9)
Age (years)											
0–4	720	889	851	884	911	816	813	736	666	810	−13.7 (− 38.6 to 11.2)
5–19	375	392	373	412	426	440	403	373	327	391	−2.7 (−13.5 to 8.1)
20–39	296	313	299	335	332	357	345	313	286	320	1.3 (−6.5 to 9.0)
40–64	274	287	282	319	320	347	337	326	297	310	5.9 (−0.8 to 12.5)
65–79	368	371	369	407	405	445	449	436	406	406	9.1 (2.4 to 15.8)
≥ 80	464	482	515	540	551	582	603	589	568	544	16.0 (9.2 to 22.8)
Out-of-hours											
Female	74	74	63	54	52	54	53	49	48	58	−3.3 (−4.7 to −1.9)
Male	56	58	49	42	40	42	40	38	37	45	−2.6 (−3.7 to − 1.6)
Age (years)											
0–4	277	283	211	175	168	146	145	130	131	185	−20.0 (− 27.3 to −12.7)
5–19	119	106	78	68	66	71	65	60	55	77	−7.0 (−10.4 to − 3.6)
20–39	80	70	54	46	45	49	48	45	45	53	−3.7 (−6.2 to −1.3)
40–64	45	42	34	29	29	32	31	30	29	33	−1.8 (−3.0 to −0.6)
65–79	36	35	27	25	22	26	25	24	24	27	−1.4 (−2.5 to − 0.4)
≥ 80	42	40	37	30	27	28	29	27	26	32	−2.1 (− 2.9 to −1.2)

and diagnosis the relative risk of antibiotic prescribing during OOH was 1.09 (95% CI 1.08 to 1.10) compared to IH. No difference was found between the two OOHCs. Age and sex adjusted relative risks of antibiotic prescribing during OOH per diagnosis were significantly higher for acute otitis media, pharyngotonsillitis, pneumonia, SSI and UTI.

For the six most common diagnoses treated with antibiotics, a comparison of treatment choice per diagnosis with IH and OOH visits was made. The prescription rate was higher during OOH for pneumonia, acute otitis media, and pharyngotonsillitis. Although the difference was statistically significant, the choices of treatment for each diagnosis were comparable between IH and OOH prescriptions (Table 6).

Discussion

During the study period, the level of infection visits was constant, but the antibiotic prescription rate decreased. Fewer prescriptions in children and for RTIs were the main reasons for the reduction. During OOH, there was a reduction both in infection visits and in antibiotic prescribing. The antibiotic prescription rate was higher during OOH than during IH, and when adjusting for age, sex, and diagnosis the difference was significant but small. The choices of treatments were similar.

Table 3 Antibiotic prescriptions according to the type of infection per 1000 inhabitants per year

	Antibiotic prescriptions per 1000 inhabitants per year										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	Average 2006–2014	Mean annual change (95% CI)
All hours											
Respiratory tract infections[a]	124	135	114	109	111	109	103	85	70	107	−6.5 (−9.0 to − 3.9)
Skin & soft tissue infections	31	32	29	33	30	32	29	30	28	30	−0.3 (−0.7 to 0.1)
Urinary tract infections	44	44	41	44	45	43	40	40	38	42	−0.7 (−1.2 to − 0.1)
Other infections[b]	4.5	4.8	4.3	4.4	4.4	4.9	3.9	3.3	3.4	4.2	−0.1 (−0.3 to 0.0)
Without infection diagnosis[c]	62	63	60	58	57	57	59	55	55	58	−0.9 (−1.4 to − 0.5)
Total all hours	266	278	248	249	247	246	236	213	194	242	−8.5 (−11.9 to − 5.2)
In-hours											
Respiratory tract infections[a]	101	109	94	93	95	93	88	73	59	89	−4.8 (−7.1 to −2.5)
Skin & soft tissue infections	26	26	25	29	26	28	26	26	24	26	−0.2 (−0.7 to 0.3)
Urinary tract infections	37	36	34	38	38	37	34	34	32	36	−0.5 (−1.1 to 0.1)
Other infections[b]	4.0	4.3	3.9	4.1	4.0	4.4	3.5	3.0	3.2	3.8	−0.1 (−0.2 to 0.0)
Without infection diagnosis[c]	55	57	55	55	54	53	55	51	50	54	−0.7 (−1.1 to − 0.3)
Total in-hours	223	233	212	219	217	216	205	186	168	209	−6.3 (−9.6 to −3.0)
Out-of-hours											
Respiratory tract infections[a]	23	26	21	16	16	16	16	12	11	17	−1.7 (−2.3 to − 1.1)
Skin & soft tissue infections	4.6	5.1	4.1	3.8	3.8	4.0	3.9	3.9	4.0	4.1	−0.1 (−0.2 to 0.0)
Urinary tract infections	7.3	7.6	6.6	5.9	6.1	5.9	6.5	5.6	6.0	6.4	−0.2 (−0.3 to 0.0)
Other infections[b]	0.4	0.5	0.4	0.3	0.5	0.4	0.4	0.3	0.3	0.4	0.0 (0.0 to 0.0)
Without infection diagnosis[c]	7.2	5.9	4.1	3.6	3.3	3.7	4.2	4.4	4.5	4.5	−0.3 (− 0.6 to 0.1)
Total out-of-hours	43	45	36	30	30	30	31	27	26	33	−2.2 (−3.3 to −1.2)

[a] Includes ear infections
[b] Includes eye infections, gastrointestinal infections, and rare infections
[c] Prescriptions with non-infection diagnosis or no diagnosis registered

This study showed that women visited primary care for infections more often than men and also received antibiotic treatment more often than men. The same pattern has been seen in other studies from Denmark, the Netherlands, and the United Kingdom [10, 27, 28]. The sex difference in the incidence of lower UTI was an important reason.

Our data on visit rates per 1000 inhabitants per years for infections were similar to the Primary Care Record of Infections in Sweden (PRIS) database [15], which consists of data since 2007 on visits with an infectious diagnosis and all antibiotic prescriptions from voluntarily participating PHCCs on an annual basis. Antibiotic prescriptions are in most cases linked to diagnoses and also includes information about age, sex, and laboratory results. The database has a larger dataset than in this study covering PHCCs in other regions but lacks OOH data. In the PRIS database, the visit rates per 1000 persons per year for infections during IH were 457 (in 2008), 441 (in 2010), and 406 (in 2013).

The total antibiotic prescribing in primary care decreased by 27% in this study. However, in the PRIS database [15] the reduction of IH antibiotic prescribing was 36%, as the IH antibiotic prescription per 1000 persons per year decreased from 245 (in 2008) to 201 (in 2010) to 157 (in 2013). For the corresponding years in our study, the IH antibiotic prescriptions per 1000 inhabitants were 212, 217, and 186, respectively. It is possible that participation in the PRIS database could have triggered a more restrictive antibiotic prescribing behaviour compared to our real-life study. A Finnish study [29] reported a 47% reduction in antibiotic prescriptions to children in primary and other out-patient care between 2010 and 2016, whereas our present study showed a 38% reduction in children in primary care between 2010 and 2014.

Several explanations are possible for the reduction in antibiotics prescriptions. For example, there might be increasing awareness among the general public that the use of antibiotics should be avoided when they are not needed. Also, physicians might have become more restrictive in prescribing. Another reason might be due to the antibiotic stewardship work performed by the Strama group, the Swedish strategic programme against

Table 4 Antibiotic prescription according to sex and age group per 1000 inhabitants per year

	Antibiotic prescriptions per 1000 inhabitants per year										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	Average 2006–2014	Mean annual change (95% CI)
All hours											
Female	249	264	231	237	233	232	218	196	173	226	−9.0 (−13.0 to −5.1)
Male	157	171	147	144	147	146	136	120	105	142	−6.3 (−9.2 to −3.5)
Age (years)											
0–4	472	562	479	440	440	357	347	281	241	402	−35.2 (−46.9 to −23.5)
5–19	240	254	208	200	209	211	197	165	134	202	−11.7 (−17.0 to −6.5)
20–39	185	192	162	163	163	169	155	135	120	160	−7.4 (−10.6 to −4.1)
40–64	168	175	147	158	155	160	146	136	119	152	−5.2 (−8.2 to −2.3)
65–79	213	211	184	199	188	195	188	174	160	190	−5.3 (−8.1 to −2.6)
≥ 80	206	206	205	196	190	188	186	182	174	192	−4.1 (−4.9 to −3.3)
In-hours											
Female	207	218	192	205	202	201	186	169	146	192	−6.7 (−10.7 to −2.8)
Male	128	139	122	124	125	125	115	102	89	119	−4.7 (−7.2 to −2.1)
Age (years)											
0–4	330	402	358	347	350	284	271	226	184	306	−22.5 (−33.3 to −11.7)
5–19	178	189	165	164	172	174	158	134	107	160	−7.5 (−12.2 to −2.9)
20–39	141	150	132	138	137	142	128	112	97	131	−5.0 (−8.1 to −1.8)
40–64	141	149	127	141	138	141	128	120	104	132	−3.9 (−6.8 to −1.0)
65–79	192	189	167	184	174	180	172	159	146	174	−4.5 (−7.1 to −1.8)
≥ 80	185	188	187	183	176	174	170	168	161	177	−3.3 (−4.2 to −2.5)
Out–of-hours											
Female	43	46	38	32	32	31	32	27	26	34	−2.3 (−3.2 to −1.3)
Male	29	32	25	21	21	21	21	18	16	23	−1.7 (−2.4 to −0.9)
Age (years)											
0–4	142	159	121	92	90	73	75	56	57	96	−12.7 (−16.7 to −8.6)
5–19	62	65	43	36	37	37	38	31	27	42	−4.2 (−6.3 to −2.1)
20–39	44	42	30	25	26	27	27	23	23	30	−2.4 (−3.8 to −1.0)
40–64	27	26	20	17	18	18	17	16	15	19	−1.4 (−2.0 to −0.7)
65–79	21	22	17	15	14	16	16	14	15	17	−0.9 (−1.5 to − 0.3)
≥ 80	21	18	18	13	13	14	16	14	13	16	−0.8 (−1.3 to − 0.2)

antibiotic resistance [30]. In 2005, Strama together with the government launched a national strategy to prevent antibiotic resistance and healthcare-associated infections. Several actions have been performed in relation to this strategy. Diagnosis-specific guidelines for optimal antibiotic use have been published and promoted, and the use of antibiotics has been reported at the local, regional, and national level [17, 31]. During 2011–2014, the Swedish government ran a patient safety campaign aiming to decrease antibiotic use with the goal of fewer than 250 annual prescriptions in out-patient care per 1000 inhabitants for all prescribers together (primary and secondary care, dental care) resulting in a decrease from 385 prescriptions (2011) to 328 prescriptions (2014) [26, 32]. Furthermore, a pneumococcal conjugate vaccine was introduced in the Swedish national vaccination programme for children in 2009. Finally, a national economic bonus system was introduced for regions achieving a reduction in the antibiotic prescription levels, and incentive for quality outcome with the same goal was introduced in 2011 at the PHCC level in Kronoberg County.

During the period studied here, the number of OOH infection visits decreased by a third. Factors contributing

Table 5 Visits and antibiotic prescriptions per diagnosis for in-hours compared to out-of-hours

Diagnoses	In-hours			Out-of-hours			
	Infection visits	Antibiotic prescriptions		Infection visits	Antibiotic prescriptions		
	Per 1000 inhabitants per year (%)	Per 1000 inhabitants per year	Percent of cases	Per 1000 inhabitants per year (%)	Per 1000 inhabitants per year	Percent of cases	Adjusted relative risk[b] (95% CI)
Respiratory tract infections	215 (56%)	89	42%	32 (62%)	17	55%	1.25 (1.24 to 1.26)
Acute bronchitis	23 (6%)	11	47%	2.2 (4%)	1.0	46%	0.95 (0.91 to 0.98)
Acute otitis media	23 (6%)	20	85%	6.7 (13%)	6.1	91%	1.01 (1.00 to 1.02)
Chronic Obstructive Pulmonary Disease	14 (4%)	2.4	18%	0.4 (1%)	0.1	34%	1.02 (0.87 to 1.19)
Influenza	1.9 (0%)	0.1	6%	0.4 (1%)	0.0	4%	0.75 (0.51 to 1.11)
Pharyngotonsillitis	28 (7%)	23	80%	6.8 (13%)	5.7	84%	1.01 (1.00 to 1.02)
Pneumonia	14 (4%)	9.1	67%	2.2 (4%)	1.7	76%	1.08 (1.05 to 1.10)
Sinusitis	17 (5%)	14	83%	1.8 (4%)	1.6	85%	1.00 (0.98 to 1.02)
Upper respiratory tract infection	81 (21%)	8.0	10%	9.6 (19%)	0.9	9%	0.87 (0.83 to 0.92)
Other respiratory tract infection	12 (3%)	2.2	18%	1.5 (3%)	0.4	27%	1.04 (0.95 to 1.14)
Skin and soft tissue infections	60 (16%)	26	44%	6.1 (12%)	4.1	68%	1.20 (1.18 to 1.23)
Urinary tract infections	45 (12%)	36	80%	7.6 (15%)	6.4	84%	1.04 (1.04 to 1.05)
Lower urinary tract infections	34 (9%)	31	90%	6.3 (12%)	5.7	89%	1.00 (1.00 to 1.01)
Other urogenital infections	10 (3%)	4.4	44%	1.3 (3%)	0.7	56%	1.07 (1.02 to 1.13)
Other infections[a]	63 (17%)	3.8	6%	6.1 (12%)	0.4	7%	0.81 (0.74 to 0.89)
Total	382 (100%)	155	41%	51 (100%)	28	55%	

[a] Includes eye infections, gastrointestinal infections, and rare infections
[b] Relative risk of antibiotic prescription adjusted for sex and age during out-of-hours compared to in-hours

to the decrease were shorter opening hours at the end of the study, a penalty fee (100 euros) introduced in 2008 for the PHCC for each patient attending the OOHC, and the introduction of a nurse triage system for walk-in patients at OOHC1.

The OOH antibiotic prescription rate per 1000 inhabitants per year was at the same level in the Netherlands, Sweden, and England (20, 28, and 31 prescriptions, respectively), but higher in Denmark (80 prescriptions) [9, 13, 27]. Two English studies have shown stable or increased OOH antibiotic prescription rates from 2010 to 2014 [8, 9]. In contrast, our study showed a decrease in antibiotic prescription rates.

The main explanation for excess prescribing during OOH is that infections that are often treated with antibiotics were more common during OOH visits such as acute media otitis, pharyngotonsillitis, and lower UTIs. The relative risk of antibiotic prescribing was decreased when adjusting for diagnoses. For SSI, the relative risk of receiving antibiotics during OOH remained elevated 1.20 (95% CI 1.18–1.23). It was uncommon to prescribe UTI antibiotics without a visit with infection diagnosis during OOH service (9% of UTI antibiotic prescriptions were without a visit during OOH compared to 39% during IH) although it was in line with current guidelines. This fully explained the higher UTI visit rate during OOH.

These results are similar to other European studies when comparing OOH and IH. A Norwegian comparison of tonsillitis and acute media otitis showed no difference in the prescription rate at OOHCs [33], and a Dutch study showed higher prescription levels during OOH for common infections and argued that the patients were sicker in the sense that they had more urgent problems that could not wait until the next day based on a revision of the EMR [13].

The remaining excess prescriptions during OOH after adjusting for diagnosis were estimated, leading to 2.2 more prescriptions per 1000 inhabitants per year compared to IH, which corresponds to 7.9% of the prescriptions during OOH and to 1.2% of all prescriptions during IH and OOH together. These prescriptions could partly be explained by sicker patients in need for urgent evaluation and an absence of control visits in the OOH setting. On the other hand, a reason could be a lower threshold to prescribe during OOH for example due to high workload or due to limited possibility to arrange for follow-ups.

Apart from the high relative risk of receiving antibiotics for SSI during OOH, there are no apparent areas to intervene. But because the total decrease of antibiotic prescriptions during the study period is 27% and the excess prescriptions during OOH are just above 1% of all antibiotic prescriptions, there

Table 6 Antibiotic treatment by antibiotic group for the six most common diagnoses between in-hours and out-of-hours

Indication	Choice of antibiotic	Prescription[a], %	
		In-hours	Out-of-hours
Acute bronchitis	Doxycycline	59%	52%
(*n* = 18,970)	Phenoxymethylpenicillin	21%	27%
	Amoxicillin	11%	11%
	Macrolides	5%	7%
	Cefadroxil	2%	2%
Acute otitis media	Phenoxymethylpenicillin[b]	70%	69%
(*n* = 41,419)	Amoxicillin	20%	21%
	Macrolides	4%	4%
	Amoxicillin/clavulanate	2%	2%
	Cephalosporins	2%	2%
Lower urinary tract infection	Pivmecillinam[b]	45%	46%
(*n* = 59,335)	Nitrofurantoin[b]	22%	20%
	Quinolones	17%	18%
	Trimethoprim	9%	7%
	Cefadroxil	5%	6%
Pharyngotonsillitis	Phenoxymethylpenicillin[b]	78%	79%
(*n* = 45,547)	Cephalosporins	9%	8%
	Clindamycin	6%	5%
	Macrolides	3%	3%
	Amoxicillin	2%	3%
	Tetracyclines	2%	1%
Pneumonia	Phenoxymethylpenicillin[b]	41%	45%
(*n* = 17,527)	Doxycycline	38%	32%
	Amoxicillin	9%	11%
	Macrolides	8%	7%
	Cefadroxil	2%	2%
Sinusitis	Phenoxymethylpenicillin[b]	54%	60%
(*n* = 23,070)	Tetracyclines	30%	25%
	Amoxicillin	9%	9%
	Macrolides	2%	2%
	Cephalosporins	3%	2%

[a] Antibiotics with prescribed percentages over 2% are shown
[b] First-choice antibiotics according to the Swedish prescribing guidelines

would be limited gain from intervening in the OOH setting.

There were no differences in treatment choice, which corresponds with other quantitative studies from Norway and the Netherlands [13, 33] and with a Belgian qualitative study where physicians reported the treatment choice to be the same as during IH, although the threshold to prescribe was lower at OOHCs [11]. In contrast, an English study noted a higher proportion of broad-spectrum antibiotics during OOH [8].

Strengths

The data set was complete for infection visits and antibiotic prescriptions in primary care in a region in Sweden. Because the whole region was included, the data were real-life data without any selection due to study participation. Also, the same EMR system was used during the study period thus decreasing the risk for information errors. Because writing a diagnosis was compulsory for all visit records, very few diagnoses were missing. All OOH infection visits and prescriptions were included, which enabled comparisons between IH and

OOH, adjusting for sex, age groups, and diagnoses. The comparison between IH and OOH is relevant for Sweden as a whole and for other countries with similar OOH settings.

Limitations

Limitations of the study include that no validation of diagnoses by examining the EMR was done. Also, the reason why some antibiotics are prescribed without a coded infection diagnosis has not been explored. A lower threshold to diagnose infections and to prescribe antibiotics in the OOH setting cannot be ruled out but would also be hard to verify in the EMR. Other antibiotics than oral and parenteral antibiotics (ATC code J01) are missing in the dataset, such as antibiotics in topical skin and eye preparations. The antibiotic rate for the elderly (> 80 years) might be underestimated due to partly missing data for patients with medication administered through a dispensing system. Furthermore, we could not measure the rate of delayed prescribing because we did not have access to pharmacy dispensing data. The common way of delayed prescribing in Sweden is that the patient receives an electronic prescription but is recommended to wait a few days before collecting the prescription [34].

Conclusions

Although the infection visit rate was unchanged, there was a significant reduction in antibiotic prescribing, especially to children and for RTIs. The increased antibiotic prescribing rate during OOH was small when adjusted for age, sex, and diagnosis, and no excess prescribing of broad-spectrum antibiotics was seen. Therefore, interventions selectively aiming at OOHCs seem to be unmotivated in a low-prescribing context.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12879-020-05334-7.

Additional file 1. Infection diagnoses selected to be included in the Kronoberg Infection Database in Primary care 2006–2014. *Description*: The total number of patients and visits are shown for all providers (physicians, nurses) and for physicians only.

Abbreviations

ATC: Anatomical therapeutic chemical classification; EMR: Electronic medical records; IH: In-hours; KIDPC: Kronoberg Infection database in primary care; OOH: Out-of-hours; OOHC: Out-of-hours centre; PHCC: Primary healthcare centre; PRIS: Primary care record of infections in Sweden database; RTI: Respiratory tract infection; SSI: Skin and soft tissue infection; UTI: Urinary tract infection

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Authors' contributions

OC and KH initiated the study. OC managed and validated the KIDPC dataset. OC carried out the analysis of the data and drafted the manuscript, which was evaluated by KH, MT, and KE. All authors critically revised and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the Regional Ethical Review Board in Linköping, Sweden to create the KIDPC database for research purposes (Dnr 2014/121–31). Permissions to extract data were obtained from all the managers of the PHCC and were included in the application of ethical approval. Confidentiality of the patients was ensured by one-way encrypted identification numbers. As this retrospective study contains only anonymous patient data, the Regional Ethical Review Board did not require informed consent from the patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Paper II

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RESEARCH

Change in the use of diagnostic tests in the management of lower respiratory tract infections: a register-based study in primary care

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Abstract

Background: Differentiating between pneumonia and acute bronchitis is often difficult in primary care. There is no consensus regarding clinical decision rules for pneumonia, and guidelines differ between countries. Use of diagnostic tests and change of management over time is not known.

Aim: To calculate the proportion of diagnostic tests in the management of lower respiratory tract infections (LRTIs) in a low antibiotic prescribing country, and to evaluate if the use and prescription pattern has changed over time.

Design & setting: A register-based study on data from electronic health records from January 2006 to December 2014 in the Kronoberg county of south east Sweden.

Method: Data regarding use of C-reactive protein (CRP), chest x-rays (CXRs), microbiological tests, and antibiotic prescriptions were assessed for patients aged 18–79 years, with the diagnosis pneumonia, acute bronchitis, or cough.

Results: A total of 54 229 sickness episodes were analysed. Use of CRP increased during the study period from 61.3% to 77.5% for patients with pneumonia (*P*<0.001), and from 53.4% to 65.7% for patients with acute bronchitis (*P*<0.001). Use of CXR increased for patients with acute bronchitis from 3.1% to 5.1% (*P*<0.001). Use of microbiological tests increased for patients with pneumonia, from 1.8% to 5.1% (*P*<0.001). The antibiotic prescription rate decreased from 18.6 to 8.2 per 1000 inhabitants per year for patients with acute bronchitis, but did not change for patients with pneumonia.

Conclusion: Use of CRP and microbiological tests in the diagnostics of LRTIs increased despite the fact that the incidence of pneumonia and acute bronchitis was stable.

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How this fits in

There are no consistent clinical decision rules for pneumonia, and guidelines regarding assessment differ between countries. Use of CRP and microbiological tests appears to be increasing in Sweden, a country with a low antibiotic prescription rate. During the same period there has been a significant reduction in antibiotics prescribed for acute bronchitis, indicating improved adherence to treatment recommendations. This emphasises the use of diagnostic testing as a piece of the puzzle in the management of lower respiratory tract infections (LRTIs).

Introduction

Diagnosis of pneumonia is a challenge for primary care physicians since there are no sharply defined clinical criteria for the diagnosis. Several efforts have been made to identify a decision rule, but results vary.[1–5] Guidelines and clinical decision rules on how to assess pneumonia in primary care differ between countries. Despite moderate sensitivity and specificity, CXR is the gold standard for the diagnosis of pneumonia.[1–6] Some guidelines recommend CXR in the initial judgment, and others recommend CRP as a complement to clinical examination.[7–9]

Swedish criteria for possible pneumonia[6] are: generally ill patient with tachypnoea (>20/min), tachycardia (>120/min), and symptoms such as fever, cough, newly expressed fatigue, and lateralised breath pain. Common findings are focally depressed or altered breathing sounds (crackles or wheezes), or dullness to percussion. CXR is not recommended in the initial judgment, nor is CRP testing. CRP can be considered when clinical diagnosis of LRTIs is unclear. Culture with resistance determination from sputum or nasopharyngeal swabs can be valuable when pneumonia is presumed, especially if the patient has been in an area with a high prevalence of bacterial resistance to antibiotics.[6]

A European study by van Vugt *et al* found that CRP >30 mg/L in conjunction with clinical examination refined the diagnostic information.[10] Previous studies have shown that CRP is widely used in this manner in Scandinavia, but not to the same extent in other countries.[11,12] Compared to most other countries, Sweden, the Netherlands, and a few other nations, have a low antibiotic prescription rate and low prevalence of antibiotic resistance in *Streptococcus pneumoniae*, the most common cause of pneumonia.[13,14] The drug of choice to treat pneumonia in Sweden is phenoxymethylpenicillin, followed by doxycycline.[6] To the authors' knowledge, if or how the management of LRTIs has changed over time has not been explored in a low prescribing country.

The aim of the present study was to calculate the proportion of CRP, CXR, and microbiological tests used in the management of LRTIs in Swedish primary care, and to evaluate if the use had changed over a period of 9 years. The secondary aim was to investigate whether the extent and pattern of antibiotic prescriptions for LRTIs had changed over the same period.

Method

Design

This is a descriptive register-based study on data from electronic health records (EHRs) between January 2006 and December 2014. Data from the EHRs are routinely transmitted to a database separate from the records. All data were extracted on one occasion. Data contained information on patients diagnosed with acute bronchitis, pneumonia, or cough, who consulted primary care in the Kronoberg county of Sweden between January 2006 and December 2014. Information on radiology and microbiological tests was not available in the EHRs before 2008.

Study population

All primary health care centres (PHCCs) in Kronoberg participated. In total, 33 PHCCs and three out-of-hours offices were included in the study and provided data through the register. Adult patients with an LRTI — pneumonia (International Classification of Diseases and Related Health Problems version 10 [ICD-10] identifier: J18.-P); acute bronchitis (ICD-10 identifier: J22.-P); and the symptom diagnosis 'cough' (ICD-10 identifier: R05.-) — were eligible for analyses. Only data from consultations for patients aged 18–79 years were included. Due to some older patients receiving dose-dispensed medications administered through a computer system without connection to the EHR, patients aged

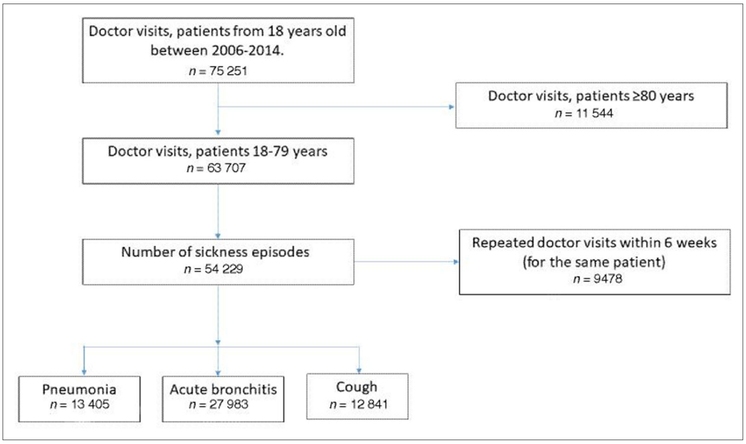

Figure 1 Flowchart of the inclusion and exclusion process

>79 years were excluded for further analyses. Contacts occurring within 6 weeks for the same patient and diagnosis were considered to be one contact (***Figure 1***).

Study variables

For each consultation the patient register provided information on sex, age at the consultation, PHCC, date, diagnoses, executed CRP tests, microbiological tests, radiography, and results of the tests performed. Information on any antibiotic prescription was also included. The Swedish primary health care version of the ICD-10 was used to identify the diagnoses.

Data analyses

Diagnoses were ranked so that the diagnosis most likely to result in an antibiotic prescription received the highest rank (pneumonia), followed by acute bronchitis and cough. Thus, if patients were diagnosed with both cough and pneumonia or acute bronchitis, cough was removed since it was considered less serious. As different devices for CRP were used at different PHCCs, the CRP values were adjusted to 8–160 mg/L (values <8 mg/L were set to 8 mg/L and values >160 mg/L were set to 160 mg/L). Proportions and medians were calculated for descriptive data. 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. Pearson's χ^2 test was used when analysing any difference in proportions. Mann-Whitney U test was used to identify any differences in skewed data. All statistical analyses were performed using IBM SPSS Statistics (version 23). *P* values <0.05 were considered significant.

Results

In total there were 75 251 visits. The number of visits excluded is presented in ***Figure 1***. After excluding patients aged ≥80 years and revisits within 6 weeks, 54 229 sickness episodes remained eligible for analyses. Among these, the median age was 55 years and 57.7% were female. Other characteristics and use of diagnostic tests are presented in ***Table 1***.

Acute bronchitis was the most common diagnosis (51.6%), followed by pneumonia (24.7%), and cough (23.7%). Of the consultations, 91.6% were made during the winter season (October–March). The proportion of CRP testing in total for pneumonia, acute bronchitis, and cough increased from 55.3% in 2006 to 61.6% in 2014 (odds ratio [OR] 1.30; 95% confidence intervals [CI] = 1.20 to 1.40; *P*<0.001). CRP was used more often when a patient was diagnosed with pneumonia (71.4%) compared to when a patient was diagnosed with acute bronchitis (61.9%; *P*<0.001). The CRP testing rate increased in the

Table 1 Characteristics of patients aged 18–79 years with lower respiratory tract infections in primary care, distribution of diagnostic tests performed, and proportion of patients prescribed antibiotics for each diagnosis

	Total (*n* = 54 229), *n* (%)	**Pneumonia (*n* = 13 405), *n* (%)**	**Acute bronchitis (*n* = 27 983), *n* (%)**	**Cough (*n* = 12 841), *n* (%)**
Median age, years	55	56	54	54
Median CRP value, g/L	14	62	11	8
Female	31 268 (57.7)	7066 (52.7)	16 890 (60.4)	7312 (56.9)
Tests performed				
CRP	33 254 (61.3)	9566 (71.4)	17 315 (61.9)	6373 (49.6)
CXR	4237 (7.8)	1657 (12.4)	1047 (3.7)	1533 (11.9)
Microbiology	1854 (3.4)	535 (4.0)	703 (2.5)	616 (4.8)
Antibiotic prescription	28 833 (53.2)	11 298 (84.3)	16 009 (57.2)	1526 (11.9)
Phenoxymethylpenicillin	8128 (15.0)	4577 (34.1)	3173 (11.3)	378 (2.9)
Doxycycline	15 954 (29.4)	4909 (36.6)	10 200 (36.5)	845 (6.6)
Amoxicillin	2469 (4.6)	832 (6.2)	1553 (5.5)	84 (0.7)
Erythromycin	1084 (2.0)	529 (3.9)	490 (1.8)	65 (0.5)
Cefadroxil	291 (0.5)	132 (1.0)	128 (0.5)	31 (0.2)
Others	906 (1.7)	318 (2.4)	465 (1.7)	123 (1.0)

CRP = C-reactive protein. CXR = chest x-ray.

diagnostics of pneumonia from 61.3% to 77.5%, as can be seen in ***Figure 2*** (OR 2.17; 95% CI = 1.83 to 2.59; *P*<0.001), and also increased in the diagnostics of acute bronchitis from 53.4% to 65.7% (OR 1.67; 95% CI = 1.50 to 1.86; *P*<0.001). For patients with pneumonia, the median CRP value was 62 mg/L (interquartiles, 27 and 107 mg/L), and did not change over time (*P* = 0.22); the median CRP value for patients with acute bronchitis was 11 mg/L (interquartiles, 8 and 29 mg/L).

Use of CXR, in total, changed from 6.8% in 2008 to 9.4% in 2014 (OR 1.45; 95% CI = 1.26 to 1.66; *P*<0.001), but did not change for the diagnosis of pneumonia (*P* = 0.36), whereas it increased

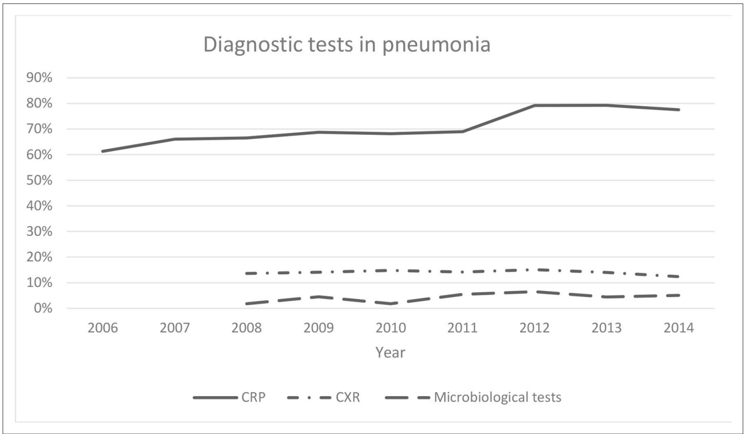

Figure 2 Proportion of patients aged 18–79 years with pneumonia in primary care, where C-reactive protein (CRP), chest x-ray (CXR), or microbiological tests were used in the diagnostic process. Data for CXR and microbiological tests was not available for 2006 and 2007.

Table 2 Prevalence of pneumonia and acute bronchitis, and antibiotics prescribed in patients aged 18–79 years in primary care (*n*/1000 inhabitants each year)

	2006	2007	2008	2009	2010	2011	2012	2013	2014
Pneumonia									
Prevalence	9.7	10.3	8.6	10.4	10.9	15.8	14.0	11.3	10.5
Antibiotics prescribed	8.2	8.7	6.9	8.7	9.1	13.5	11.8	9.5	9.1
Acute bronchitis									
Prevalence	25.2	26.5	23.0	20.7	21.8	26.9	25.7	23.0	20.7
Antibiotics prescribed	18.6	19.1	15.3	12.5	12.0	14.3	12.9	10.5	8.5

from 3.1% in 2008 to 5.1% in 2014 (OR 1.68; 95% CI = 1.29 to 2.18; *P*<0.001) for the diagnosis of acute bronchitis. Use of CXR also increased in the diagnosis of cough (OR 1.47; 95% CI = 1.16 to 1.19; *P*<0.05). When CXR was performed for patients with pneumonia or acute bronchitis, CRP was analysed in 81.1% of the cases.

In total, microbiological testing increased (OR 2.26; 95% CI = 1.82 to 2.81; *P*<0.001). This was performed in 4.5% of patients with pneumonia. The most common microbiological analysis was polymerase chain reaction for *Mycoplasma pneumoniae* from nasopharyngeal aspirates (2.5%), followed by nasopharyngeal swabs (0.9%) for culture of bacteria. Use of microbiological tests increased from 1.8% in 2008 to 5.1% in 2014 in the diagnostics of pneumonia (OR 2.9; 95% CI = 1.8 to 4.8; *P*<0.001) and from 1.5% to 4.1% in the diagnostics of acute bronchitis (OR 2.9; 95% CI = 2.1 to 4.1; *P*<0.001) during the same period.

The prevalence of different diagnoses and antibiotics prescribed during the study period are presented as *n*/1000 inhabitants per year (***Table 2***). The antibiotic prescription rate for patients with pneumonia was 84.3% in total and did not change (OR 1.11; 95% CI = 0.89 to 1.38; *P* = 0.38). For patients with acute bronchitis, the antibiotic prescription rate decreased from 73.6% in 2006 to 41.0% in 2014 (OR 0.25; 95% CI = 0.22 to 0.28; *P*<0.001). The significance persisted when adjusting for age, sex, and PHCC in a multiple logistic regression model. Change of antibiotic prescription rate over time is shown in ***Figure 3***. The proportion of phenoxymethylpenicillin prescribed for patients with pneumonia increased (OR 1.9; 95% CI = 1.6 to 2.3; *P*<0.001) and amoxicillin and erythromycin

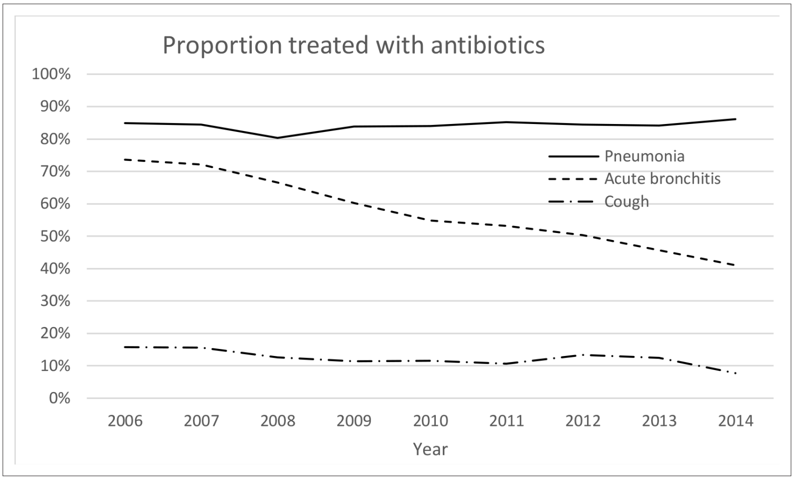

Figure 3 Proportions of patients aged 18–79 years with lower respiratory tract infections and cough treated with antibiotics in primary care

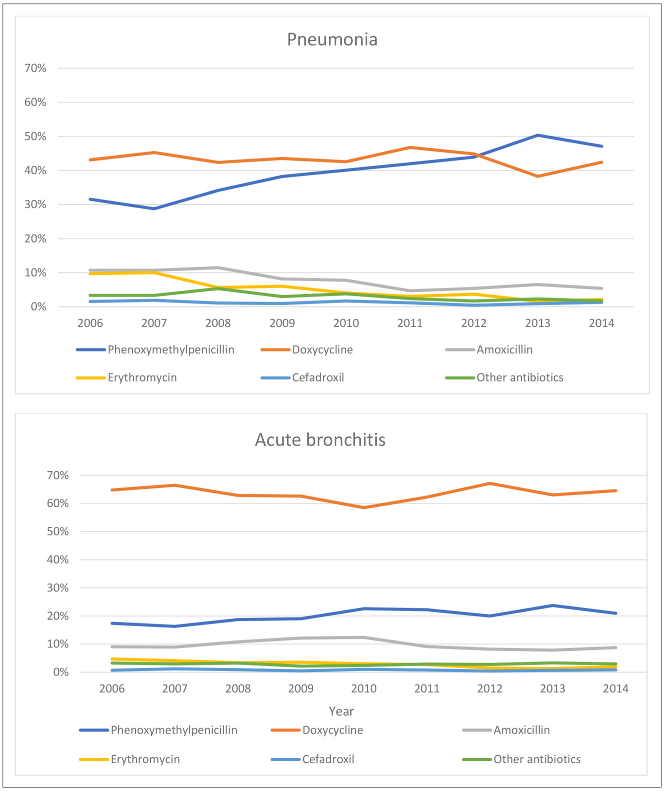

Figure 4 Distribution of antibiotic prescriptions for pneumonia and acute bronchitis in patients aged 18–79 years in primary care

decreased ($P<0.001$), whereas the proportion of doxycycline prescribed did not change ($P = 0.74$) as shown in ***Figure 4***. When narrow-spectrum respiratory antibiotics (phenoxymethylpenicillin and amoxicillin) were prescribed for patients with pneumonia, the median CRP value was higher (72 mg/L) compared to when broad-spectrum respiratory antibiotics (doxycycline and erythromycin) were prescribed (50 mg/L) ($P<0.001$).

Discussion

Summary

This register-based study on LRTIs shows that the use of CRP testing increased from 53.4% to 65.7% in the assessment of patients with acute bronchitis and from 61.3% to 77.5% for patients with pneumonia from January 2006 to December 2014. For patients with acute bronchitis, the use of CXR increased and the proportion of microbiological tests was low but increased significantly for both patients with pneumonia and patients with acute bronchitis. To the authors' knowledge, the change in the use of diagnostic tests for the diagnosis of LRTIs in primary care over time has not been shown before.

There was a significant reduction in antibiotics prescribed for acute bronchitis, whereas the proportion of phenoxymethylpenicillin prescribed for pneumonia increased. Thus, adherence to treatment recommendations regarding assessment of LRTIs improved.

Strengths and limitations

The large study size and the fact that data are from a whole county are strengths, minimising the risk of selection bias. The documentation of the tests performed is likely to be reliable and reflects the daily work at PHCCs. As the register is complete for primary care, there is no risk of data loss due to, for example, private surgeries. The authors decided to include the symptom diagnosis 'cough' to cover possible cases where physicians were uncertain of the diagnosis and patients could have been treated with antibiotics, and in that way were concealed by the diagnosis. This is a strength, and it appeared that the proportion of antibiotics prescribed for this group was low.

There are some limitations that need to be discussed. First, antibiotic prescriptions are based on those made in the EHRs. Although the authors excluded patients aged ≥80 years, there are likely to have been some younger patients who were prescribed antibiotics through a dose-dispensing system not accessible in the EHRs. Furthermore, patients with severe pneumonia were likely to have been admitted to hospital and treated with antibiotics in that context, and therefore would not have had a prescription from a PHCC. There might also have been some patients who were diagnosed with pneumonia when followed up in primary care after hospitalisation, even though visits within 6 weeks from the first consultation were excluded; therefore, they would not have had a prescription related to the contact. This could explain the somewhat low antibiotic prescription rate in the pneumonia group.

Comparison with existing literature

Use of CRP is known to be frequent in the assessment of respiratory infections in Scandinavia, but it is not recommended in the initial judgment of pneumonia in primary care.[6,12,15] In the present study, CRP testing increased and the frequency was high (71.4%) compared to a 2009 Swedish study by Engström *et al*, in which the corresponding frequency was only 38% in pneumonia diagnosis, and another 2016 study by Tyrstrup *et al* in which the testing rate was 60.4%, indicating that usage of point of care CRP has progressively increased.[16,17] Earlier studies have shown that assessment of pneumonia differs between countries. For example, CRP testing is more widely used in Denmark compared to Spain, where CXR is more often used in the judgment.[11]

The incidence of pneumonia varies between 5 and 11 cases per 1000 inhabitants a year in different studies.[18,19] The present study showed a relatively high annual incidence of pneumonia, ranging from 8.6 to 15.8/1000 inhabitants a year. The highest incidence was in 2011 when there was a *M. pneumoniae* outbreak.

When diagnostic tests are used in Swedish primary care, the PHCC not the GP is charged for the costs, which could explain the high testing frequency. Use of CRP testing has also been questioned, and one study by van Vugt *et al* showed that low values do not exclude radiographic pneumonia, whereas a study by Lagerström *et al* suggested that CRP testing can help to exclude pneumonia.[10,20]

The median CRP found in patients with pneumonia (62 mg/L) might be considered as low compared to, for example, the National Institute for Health and Care Excellence guidelines, but according to Swedish guidelines, pneumonia should be considered if CRP is >100 mg/L at the visit, or >50 mg/L after 1 week of duration.[8] CRP is probably just a piece of the puzzle in the total judgment of the LRTI patient; however, information on the symptom duration is lacking.

Looking at the interquartiles of the CRP level for pneumonia and acute bronchitis is interesting. The lower interquartile for CRP in patients with pneumonia was 27 mg/L and the higher interquartile for CRP in patients with acute bronchitis was 29 mg/L, suggesting that CRP above 30 mg/L constitutes some kind of limit for diagnosing pneumonia, in line with the European study by van Vugt *et al.*[10]

The present study indicates that the antibiotic prescription pattern has changed over time and the proportion of prescribed phenoxymethylpenicillin, the drug of choice, has increased for the treatment of pneumonia in recent years. It is also encouraging that the antibiotic prescription rate for acute bronchitis has diminished from 73.6% to 41.0%, since guidelines do not recommend antibiotic treatment for this condition.[6] This differs from the prescription rate for acute bronchitis in the US, where it appears to increase, and from Denmark, where the prescription rate is much lower according to a recent study by Saust *et al.*[21,22] The efforts made by the Swedish strategic programme against antibiotic resistance (STRAMA) to illuminate the problem of resistant bacteria and to increase awareness of antibiotic resistance might have influenced the prescription pattern. It may also have increased the awareness of antibiotic resistance and contributed to increased knowledge.[23,24]

The low rate of microbiological testing is not surprising; however, the authors observed a threefold increase during the study period. The physician's concern for *M. pneumoniae* and heightened awareness of antimicrobial resistance in general is likely to be a contributory explanation for the increase.

The use of CXR was stable for pneumonia but increased for acute bronchitis. The overall CXR rate for pneumonia was 12.4% in contrast to Saust *et al*'s Danish study, where CXR was used for 7.2% of the patients; however, that study included patients of all ages.[22]

Implications for research and practice

In the present study, doxycycline was, in divergence with guidelines, prescribed surprisingly frequently for patients with pneumonia and was associated with lower CRP levels. An explanation could be that physicians may have suspected a probability of atypical bacterial infections, such as *M. pneumoniae*. This might reflect a need for further interventions in this respect, indicating that efforts made so far have not fully managed to capture any concerns of atypical bacterial infections.[25] In the present study, the authors do not know enough about any comorbidities that might have played a role in the choice of treatment. Furthermore, the choice of antibiotics could also indicate knowledge gaps among the prescribers.[26]

Since CRP testing is increasing and the prescription rate for acute bronchitis is decreasing at the same time, this might indicate that CRP is more often used to ensure the diagnosis of acute bronchitis and, in cases of acute bronchitis, motivate the choice to refrain from prescribing antibiotics. The increasing use of both CRP and microbiological tests in diagnosing pneumonia might reflect the absence of clear diagnostic criteria and possibly a perceived need for diagnostic tests in primary care.

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Ethical approval

The study was approved by the regional ethic review board in Linköping (Dnr 2014/121-31).

Provenance

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Paper III

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RESEARCH ARTICLE

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Factors influencing antibiotic prescribing for respiratory tract infections in primary care – a comparison of physicians with different antibiotic prescribing rates

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ABSTRACT

Background: There has been a notable decrease in antibiotic prescribing in the last thirty years in Sweden. Little is known about factors influencing antibiotic prescribing over several years.
Objective: To compare primary care physicians who, over time, reduced their antibiotic prescribing for respiratory tract infections with those who remained either high or low prescribers regarding potentially influencing factors.
Design and setting: A register-based study including all RTI visits in primary care in Region Kronoberg, Sweden 2006–2014. The data were divided into three 3-year periods.
Subjects: The data comprised all physicians who had diagnosed at least one RTI for each of the three-year periods. The antibiotic prescribing rate adjusted for the patients' sex and age group was calculated for each physician and period, and based on the change between the first and the third period, the physicians were divided into three prescriber groups: The High Prescribing Group, the Decreasing Prescribing Group, and the Low Prescribing Group.
Main outcome measures: For the three prescriber groups, we compared factors influencing antibiotic prescribing such as the characteristics of the physicians, their use of point-of-care tests, their choice of diagnoses, and whether the patients returned and received antibiotics.
Results: The High Prescribing Group ordered more point-of-care tests, registered more potential bacterial diagnoses, prescribed antibiotics at lower C-reactive protein levels, and prescribed antibiotics more often despite negative group A Streptococci test than in the Low Prescribing Group. The Decreasing Prescribing Group was between the High Prescribing Group and the Low Prescribing Group regarding these variables. The lower prescription rate in the Low Prescribing Group did not result in more return visits or new antibiotic prescriptions within 30 days.
Conclusion: Point-of-care testing and its interpretation differed between the prescriber groups. Focus on interpreting point-of-care test results could be a way forward in antibiotic stewardship.

KEY POINTS

- High prescribers used antibiotics at lower CRP levels and were more likely to identify a potential bacterial diagnosis.
- Many physicians reduced their antibiotic prescribing during the study period. Nine out of ten low prescribers remained low prescribers.
- Seeing a low-prescribing physician did not lead to more return visits or antibiotic changes.

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Antibiotic prescribing; diagnosis-linked prescription; infectious disease; physicians' behaviour; point-of-care testing

Introduction

Since antimicrobial resistance is a severe threat to global public health, the World Health Organization adopted in 2015 a global action plan [1]. The reduction of over-prescribing of antibiotics is an important factor in limiting antibiotic resistance [2]. However, there is still a considerable variation between physicians, regions, and countries in the use of antibiotics for infections in primary care, indicating that the optimal level is not yet reached [3–7].

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High antibiotic prescribing has been associated with older physicians, higher patient volume, and longer time in practice [8–11]. High antibiotic prescribing frequency has also been associated with rural primary health care centres [11] and areas with low socioeconomic status [12]. However, these factors have limited explanatory power. Therefore, other factors such as diagnostic uncertainty, perceived severity of the illness, patients' expectations, physicians' perceptions of patients' expectations, and communication skills have been suggested [13]. Nonetheless, the reasons for different antibiotic prescribing habits amongst physicians are unclear.

In the last three decades, there has been a decrease in antibiotic prescribing in Swedish primary care, especially for respiratory tract infections (RTI) and for children [7]. Antibiotic stewardship, pneumococcal conjugate vaccination, and public awareness are possible explanations [14,15]. It is unknown whether there is an even reduction in antibiotic prescribing in primary care among all physicians or if only some physicians have reduced their prescribing.

Most studies on antibiotic prescribing have been either cross-sectional or qualitative [13]. No study has, over time, compared physicians who reduce their prescribing of antibiotics to those who stay high prescribers. Understanding why some physicians continue to be high prescribers could facilitate future interventions.

The aim was to compare primary care physicians who, over time, reduced their antibiotic prescribing for respiratory tract infections with those who remained either high or low prescribers regarding potentially influencing factors. Primarily, factors influencing antibiotic prescribing rates were investigated such as physicians' characteristics, the use of point-of-care tests and the choice of diagnoses. Secondly, the consequences of the different antibiotic prescribing rates were investigated, including return visit rate and renewed antibiotic prescribing.

Materials and methods

The data in the present study have been extracted from a larger dataset, the Kronoberg Infection Database of Primary Care (KIDPC) [14]. In summary, the KIDPC dataset features all infection visits and all antibiotic treatments in primary care at 33 primary health care centres (PHCCs) and three out-of-hours offices in Kronoberg Region, Sweden, 2006–2014. During each visit, the physicians must register at least one diagnostic code according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or its modified Swedish PHC edition (KSH97-P). RTIs consist of the following diagnosis groups: acute bronchitis, acute media otitis, exacerbation of COPD, influenza, pharyngotonsillitis, pneumonia, sinusitis, upper RTI, and other RTIs (Supplemental Table 1). Antibiotic prescriptions were identified according to Anatomical Therapeutic Chemical Classification (ATC) code group J01, which includes all oral and parenteral antibiotics but not antibiotics in ointments or eye drops. Antibiotic prescriptions were included if linked to RTI diagnoses, i.e. if prescribed on the same day and at the same PHCC. The data in the KIDPC were extracted from the electronic medical records in Kronoberg County (Cambio Cosmic software, Cambio Healthcare Systems AB, Linköping, Sweden) on one occasion in 2015 using Business Objects (SAP AG, Walldorf, Germany).

In the present study, data on RTI visits were extracted from the KIDPC database, including information about the patient (age, sex), the physician (age, sex, training level), the PHCC, the investigations (C-reactive protein (CRP) test and rapid antigen detection test (RADT) for Group A Streptococci (GAS)), and the antibiotic treatment.

The data were divided into three 3-year periods. All 166 physicians who had diagnosed at least one RTI during each of the three periods were identified. On the other hand, 847 physicians had not been active during all three periods and were excluded at this stage. These were locums, interns not continuing in family medicine, and physicians who moved or retired.

The antibiotic prescribing rate was defined as the number of antibiotic prescriptions at RTI visits divided by the number of RTI visits. The antibiotic prescribing rates for RTIs per 3-year period were calculated for each physician and were adjusted for the patients' sex and age group.

The physicians were divided into prescriber groups in three steps. Firstly, they were classified into three equal levels based on their antibiotic prescribing rate during the first period, 2006–2008. Low-level prescribers were defined as having an antibiotic prescribing rate below 40%, medium-level prescribers as having an antibiotic prescribing rate between 40 and 48%, and high-level prescribers as having an antibiotic prescribing rate over 48%. Secondly, during the third period, 2012–2014, the physicians were again divided into three levels using the same cut-offs.

Finally, in the third step, three prescriber groups were identified: The High Prescribing Group (consisting of high- or medium-level prescribers during both the first and the third period), the Decreasing Prescribing Group (consisting of high- or medium-level prescribers during the first period who transitioned to low-level prescribers during the third period), the Low Prescribing Group (consisting of low-level prescribers during both the first and the third period). Five physicians who were low-level prescribers during the first period and were medium- or high-level prescribers during the third period were excluded from further analyses as they did not fit in with the predefined prescriber groups (Figure 1).

The remaining 161 physicians were included and had 263,000 RTI visits, corresponding to 66% of all RTI visits in the region. In all, they had prescribed 108,000 antibiotic prescriptions at RTI visits, corresponding to 66% of all RTI antibiotic prescriptions in the region (Table 1).

The following characteristics of the physicians were used in the analyses: sex, birthyear, training level (specialist in family medicine during 0%, 1–49%, 50–99% or 100% of the infection visits), continuity (number of PHCC at which each physician has worked), out-of-hours rate (out-of-hours visits per total number of visits per physician), and activity level (total number of RTI visits).

An RTI visit was defined as an index visit if there was no RTI visit in the previous 30 days. A return visit was defined as an RTI visit within 1–30 days of an earlier RTI visit. Antibiotics at return visits were defined if antibiotics were prescribed at a return visit within

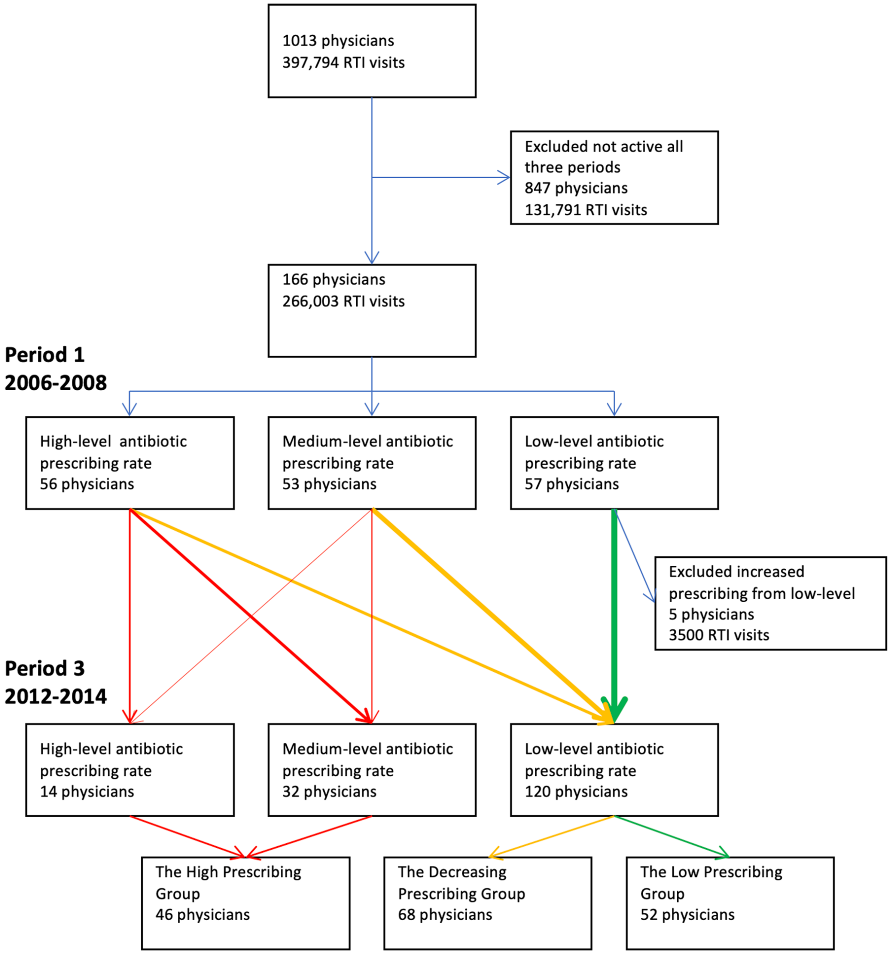

Figure 1. Flow chart showing the inclusion process and division into prescriber groups based on change of antibiotic prescription rate for respiratory tract infections (RTI) between the first period 2006–2009 and the third period 2012–2014.

Table 1. Background information on primary care physicians, respiratory tract infections, and antibiotic prescriptions for included and excluded physicians during the study period 2006–2014.

		Physicians	
		Included	Excluded
		$n = 161$	$n = 852$
Physicians		*n* (%)	*n* (%)
Sex	Female	63 (39)	169 (20)
	Male	88 (55)	194 (23)
	Unknown	10 (6)	489 (57)
Birth year	≤1940s	34 (21)	43 (5)
	1950s	45 (28)	43 (5)
	1960s	45 (28)	65 (8)
	1970s	24 (15)	88 (10)
	>1980s	3 (2)	124 (15)
	Unknown	10 (6)	489 (57)
Training level			
Specialist in family medicine during	100% of visits	70 (43)	273 (32)
	50 to <100% of visits	41 (25)	38 (4)
	1 to <50% of visits	30 (19)	32 (4)
Junior physician or other specialist		20 (12)	509 (60)
Continuity – number of primary health care centres at which each physician has worked	1	28 (17)	564 (66)
	2	43 (27)	186 (22)
	3–4	50 (31)	80 (9)
	5+	40 (25)	22 (3)
Respiratory tract infections		***n* (% of RTI visits)**	***n* (% of RTI visits)**
Total visits		262,503 (100)	135,291 (100)
Out-of-hours visits		40,431 (15)	11,757 (9)
Index visits		220,979 (83)	114,469 (87)
Antibiotic prescriptions		107,767 (41)	56,509 (42)
Antibiotic prescriptions at index visits		91,859 (35)	48,463 (37)
Point-of-care testing for respiratory tract infections			
C-reactive protein test		104,361 (40)	60,665 (45)
Rapid antigen detection test for Group A *Streptococci*		50,253 (19)	33,584 (25)
Number of respiratory tract infections visits per physician			
		RTI visits, *n*	**RTI visits, *n***
	10th percentile	259	6
	median	1630	52
	90th percentile	2925	406

RTI: respiratory tract infection.

30 days of an index visit. These measures were linked to the physician of the index visit. The use and result of point-of-care tests (CRP and RADT) and diagnoses at index visits were also measured. These measures are reported in two ways: (1) numbers per index visits per prescriber group (group level), and (2) numbers per physician per prescriber group (physician level). In the latter case, the data were divided into quartiles.

Continuous variables with non-normal distribution were presented as medians (interquartile range, IQR), and the Median test was used to compare medians across groups. Continuous variables with normal distribution were presented as means with standard deviation (SD), proportions and rates per physician. The characteristics of the physicians, investigations, diagnoses, treatment, and follow-up were analysed at the group level using Pearson's χ^2 test to compare groups and Cramer's V to measure the effect size. At the physician level, the data were divided into quartiles and the prescriber groups were compared using Pearson's χ^2 test. If the comparisons of the three prescriber groups were statistically significant, pairwise comparisons were conducted using Bonferroni correction (multiplying *p* values with three) to account for multiple analyses. To compare the High Prescribing Group with the Decreasing Prescribing Group, multiple logistic regression with a full model was performed using background factors (physicians' sex and birth year) and selected variables that were significant in a univariate logistic regression as independent variables. All statistical analyses were performed using IBM SPSS Statistics (version 27). *p* Values <0.05 were considered significant.

Results

General development

There was a general reduction in antibiotic prescribing for RTI per physician. The mean adjusted antibiotic prescribing rate for RTI per physician decreased from 45% (SD 16%) during the first period to 35% (SD 13%) during the third period. When comparing the first and third periods 84% (139/166) of the prescribers decreased their antibiotic prescribing rate. The Decreasing Prescribing Group consisted of 62% (68/109) of the medium- and high-level prescribers during the first period that became low-level prescribers in the third period. The High Prescribing Group consisted of 38% (41/109) of the medium- and high-level prescribers during the first period who remained medium- or high-level prescribers in the third period. Finally, the Low Prescribing Group consisted of 91% (52/57) of the low-level prescribers during the first period who remained low-level prescribers in the third period, and 9% (5/57) of the low-level prescribers during the first period became medium- or high-level prescribers in the third period and were excluded from further analyses. See Figure 1.

Characteristics of physician

The only significant difference when comparing the three prescriber groups was the number of RTI visits, where a lower frequency was more common in the Low Prescribing Group. No significant differences were found in physicians' sex, birth year, training level, continuity, and out-of-hours work (Table 2).

Point-of-care testing

All the analyses of point-of-care testing were limited to index visits.

At the group level, CRP tests were analysed in 36% of the index visits in the Low Prescribing Group, 39% in the Decreasing Prescribing Group, and 44% in the High Prescribing Group ($p < 0.001$, Cramer's V 0.06). Between the first and the third period the CRP test use increased from 37 to 43% of the index visits, and the increase was observed in all three prescriber groups. The median CRP values for all CRP tests were the same (10 mg/L) for the three prescriber groups ($p = 0.073$), but when antibiotics were prescribed the median CRP values differed: 45 mg/L (IQR 15–82) in the Low Prescribing Group, 33 mg/L (IQR 10–67) in the Decreasing Prescribing Group, and 23 mg/L (IQR 6–53) in the High Prescribing Group ($p < 0.001$). The result was similar although not significant when limiting to index visits with a diagnosis of pneumonia.

Rapid antigen detection test (RADT) for Group A Streptococci (GAS) was used in 20% of the index visits at the group level. The RADT use (tests per index visit) was 16% in the Low Prescribing Group, 19% in the Decreasing Prescribing Group, and 26% in the High

Table 2. Comparison of characteristics of the primary care physicians in the prescriber groups (the Low Prescribing Group, the Decreasing Prescribing Group, and the High Prescribing Group).

		Prescriber groups			
		Low Prescribing Group	Decreasing Prescribing Group	High Prescribing Group	*p*-Value
Primary care physicians' characteristics		*n* (%)	*n* (%)	*n* (%)	
Physicians' sex	Female	16 (36)	31 (46)	16 (41)	0.53
	Male	29 (64)	36 (54)	23 (59)	
Physicians' birth year	≤1940s	13 (29)	12 (18)	9 (23)	0.28
	1950s	9 (20)	26 (39)	10 (26)	
	1960s	13 (29)	17 (25)	15 (38)	
	≥1970s	10 (22)	12 (18)	5 (13)	
Training Level					
Specialist in Family Medicine	100% of visits	20 (38)	36 (53)	14 (34)	0.24
	50 to <100% of visits	14 (27)	15 (22)	12 (29)	
	1 to <50% of visits	8 (15)	11 (16)	11 (27)	
Junior physician or other specialist		10 (19)	6 (9)	4 (10)	
Physicians' continuity – number of primary health care centres at which each physician has worked	1	12 (23)	10 (15)	6 (15)	0.3
	2	16 (31)	21 (31)	6 (15)	
	3-4	14 (27)	23 (34)	13 (32)	
	≥5	10 (19)	14 (21)	16 (39)	
Physicians' out-of-hours rate – Out-of-hours visits per total number of visits per physician	0%	13 (25)	5 (7)	7 (17)	0.084
	0.1 to <10%	13 (25)	16 (24)	13 (32)	
	10 to <20%	19 (37)	32 (47)	11 (27)	
	≥20%	7 (13)	15 (22)	10 (24)	
Physicians' activity level - number of respiratory tract infection visits in total per physician	≤900	23 (44)	9 (13)	8 (20)	0.006*
	901–1600	8 (15)	19 (28)	12 (29)	
	1601–2300	14 (27)	20 (29)	12 (29)	
	>2300	7 (13)	20 (29)	9 (22)	

The variables are based on data for all nine years and assigned to the physician of the index visit.
*The comparison between the Low Prescribing Group and the Decreasing Prescribing Group was significant at $p < 0.001$. No other pairwise comparison was significant.

Prescribing Group. 95% of cases with positive RADT received antibiotics ($p < 0.001$, Cramer's V 0.09). Between the first and the third period, the use of RADT increased from 20 to 21% during the index visits, where the increase was observed in the High Prescribing Group but not in the Low Prescribing Group. Patients with a negative RADT also received antibiotics in some cases: 15% of cases with negative RADT in the Low Prescribing Group, 22% in the Decreasing Prescribing Group, and 35% in the High Prescribing Group ($p < 0.001$, Cramer's V 0.175). The result was also significant when limiting to index visits, resulting in a diagnosis of pharyngotonsillitis.

Diagnoses

At the group level, the diagnosis code for upper RTI was selected for index visits in 46% of the Low Prescribing Group, 38% in the Decreasing Prescribing Group, and 29% in the High Prescribing Group ($p < 0.001$, Cramer's V 0.13). Between the first and the third period, the diagnosis of upper RTI increased from 37 to 38% of the index visits. There was an increase in the Decreasing Prescribing Group (from 37 to 38%) and the High Prescribing Group (from 27 to 31%) but a reduction in the Low Prescribing Group (from 48 to 44%). An opposite pattern was seen for pharyngotonsillitis, acute media otitis and sinusitis where the diagnoses were more frequent in the High Prescribing Group (Supplemental Table 2).

Follow-up

Return visits within 30 days occurred in 14% of the Low Prescribing Group, 14% in the Decreasing Prescribing Group, and 15% in the High Prescribing Group ($p < 0.001$, Cramer's V 0.009). If antibiotics were prescribed at the index visit, return visits occurred in 16% of index visits in all prescriber groups ($p = 0.64$).

Antibiotics were prescribed a second time within 30 days in 6.0% of the index visits in the Low Prescribing Group, 6.1% in the Decreasing Prescribing Group, and 6.6% in the High Prescribing Group ($p < 0.001$, Cramer's V 0.01). If antibiotics were prescribed at the index visit, there was no difference in the proportion of second antibiotic prescriptions between the prescriber groups ($p = 0.40$).

Comparison at the physician level

The use and result of different tests, the selection of diagnoses, and the rate of return visits and antibiotics within 30 days are shown per physician per prescriber group in Table 3. Compared with the group level the pattern was similar. Prescribers belonging to the High Prescribing Group used antibiotics at lower median CRP values and treated more patients with negative RADT for GAS with antibiotics. They were also more likely to select a diagnosis with potential bacterial aetiology. The Decreasing Prescribing Group had a lower return visit rate within 30 days compared to the High Prescribing Group. The antibiotic prescribing rate at return visits within 30 days was similar between the groups.

Comparison of the Decreasing Prescribing Group and the High Prescribing Group

To study factors of importance for belonging to the Decreasing Prescribing Group compared to the High Prescribing Group we included in a multiple regression model the physicians' age, sex, and continuity, as well as the variables that emerged as significant in the groupwise comparison. Odds ratios for belonging to the High Prescribing Group compared to the Decreasing Prescribing Group (index group) were analysed. Two variables remained significant in the adjusted model: Physicians in the High Prescribing Group were more likely to select a diagnosis with potential bacterial aetiology and to prescribe antibiotics to patients with negative RADT for GAS (Table 4). A sensitivity analysis where physicians with less than 50 RTI visits were omitted showed similar results.

Discussion

This register-based study showed differences between the prescriber groups regarding the use and interpretation of point-of-care tests and the likelihood of registering a diagnosis with potential bacterial aetiology. Compared to the Low Prescribing Group, the High Prescribing Group ordered more CRP testing, prescribed antibiotics at lower CRP levels, ordered more RADT for GAS, and prescribed antibiotics more often when negative RADT. Also, the High Prescribing Group was more prone to register a diagnosis with potential bacterial aetiology than the Low Prescribing Group. Regarding these parameters, the Decreasing Prescribing Group was between the High and the Low Prescribing Group.

The lower antibiotic prescribing rate at index visits in the Low Prescribing Group did not result in more return visits or antibiotic prescriptions within 30 days. There were no differences in physicians' characteristics between the prescriber groups besides that having few RTI visits was more common in the Low Prescribing Group.

Table 3. Comparison of the prescriber groups (the Low Prescribing Group, the Decreasing Prescribing Group, and the High Prescribing Group) by physicians' use of point-of-care tests, their choice of diagnosis, and how often the patients returned and received antibiotics.

		Prescriber groups			*p*-Value			
		Low Prescribing Group *n* (%)	Decreasing Prescribing Group *n* (%)	High Prescribing Group *n* (%)	All	Low vs. Decreasing Prescribing Group[a]	Decreasing vs. High Prescribing Group[a]	Low vs. High Prescribing Group[a]
CRP test use at index visits (% of index visits)	<26%	17 (33)	17 (25)	7 (17)	0.463			
	26 to <40.2%	12 (23)	19 (28)	9 (22)				
	40.2 to <52.7%	9 (17)	17 (25)	14 (34)				
	≥52.7%	14 (27)	15 (22)	11 (27)				
Median CRP test result at index visits per physician (mg/L)	<9.5	14 (27)	22 (32)	14 (34)	0.881			
	9.5–11.5	17 (33)	25 (37)	16 (39)				
	12	6 (12)	7 (10)	4 (10)				
	≥13	15 (29)	14 (21)	7 (17)				
Median CRP test result at index visits per physician where antibiotics were prescribed (mg/L)	<24	6 (12)	14 (21)	22 (54)	<0.001	0.022	0.001	<0.001
	24–36	6 (12)	20 (29)	14 (34)				
	37–46	17 (33)	21 (31)	3 (7)				
	≥46.5	23 (44)	13 (19)	2 (5)				
Median CRP test result at index visits with pneumonia where antibiotics were prescribed per physician (mg/L)	<59	11 (22)	12 (18)	17 (42)	0.059			
	59–75	10 (20)	19 (28)	10 (25)				
	75.5–96.5	16 (32)	19 (28)	4 (10)				
	≥97	13 (26)	17 (25)	9 (22)				
RADT use for GAS at index visits	<13%	19 (37)	18 (26)	4 (10)	0.001	1.000	0.021	0.001
	13 to <19%	11 (21)	19 (28)	10 (24)				
	19 to <25.9%	15 (29)	18 (26)	7 (17)				
	≥25.9%	7 (13)	13 (15)	20 (49)				
Negative RADT result for GAS at index visits where antibiotics were prescribed (% of tested)	<23%	20 (38)	19 (28)	2 (5)	<0.001	1.000	<0.001	<0.001
	23 to <34%	15 (29)	19 (28)	5 (12)				
	34 to <48%	9 (17)	20 (29)	12 (29)				
	≥48%	8 (15)	10 (15)	22 (54)				
Negative RADT result for GAS at index visits with pharyngotonsillitis where antibiotics were prescribed (% of tested)	<11%	22 (42)	13 (19)	5 (11)	0.001	0.153	0.099	0.003
	11 to <23%	13 (25)	22 (32)	5 (11)				
	23 to <33%	9 (17)	18 (26)	17 (39)				
	≥33	8 (15)	15 (22)	17 (39)				
The likelihood of selecting a diagnosis with potential bacterial aetiology[b] (% of index visits)	<33%	27 (52)	12 (18)	2 (5)	<0.001	<0.001	<0.001	<0.001
	33.0 to <37.3%	17 (33)	22 (32)	1 (2)				
	37.3 to <43.5%	4 (8)	27 (40)	9 (22)				
	≥43.5%	4 (8)	7 (10)	29 (71)				
Return visits within 30 days (% of index visits)	<13.0%	15 (29)	15 (22)	11 (27)	0.029	0.696	0.015	1.000
	13.0 to <14.3%	13 (25)	19 (28)	7 (17)				
	14.3 to <15.3%	11 (21)	24 (35)	6 (15)				
	≥15.3%	13 (25)	10 (15)	17 (41)				
Antibiotics at return visits within 30 days (% of index visits)	<5.4%	15 (29)	16 (24)	10 (24)	0.419			
	5.4 to <6.1%	10 (19)	22 (32)	8 (20)				
	6.1 to <6.8%	16 (31)	15 (22)	9 (22)				
	≥6.8%	11 (21)	15 (22)	14 (34)				

The variables are based on data for all nine years and assigned to the physician of the index visit. The variables are divided into quartiles.
CRP: C-reactive protein; GAS: Group A *Streptococci*; RADT: rapid antigen detection test.
[a] *p*-Value adjusted for pairwise comparison with Bonferroni correction by multiplying with three.
[b] Diagnoses with potential bacterial aetiology: acute media otitis, pharyngotonsillitis, pneumonia, and sinusitis.

Strengths

The physicians were followed up for nine years at individual and group levels. During the study period, the same electronic medical record system was used in all the PHCCs in the region, including out-of-hours offices. The dataset is, therefore, comprehensive for primary care in the region. The study was performed before the development of telehealth services, which means that the risk of missing visits made in other regions via telehealth services is low. It would be difficult to replicate the study today. 78% of all antibiotic prescriptions were linkable to an infection diagnosis, which is a high level compared to a study from England [14,16].

Limitations

Other models could have been chosen to divide the physicians into groups. However, the aim was to study physicians who reduced their antibiotic prescribing rate. Thirteen physicians had less than ten RTI visits in either the first or the third period which makes the antibiotic prescribing rate inexact (Four physicians had less than five RTI visits in either period). Information regarding age and sex is missing for a few physicians, and this could affect the absence of differences. Possible confounders such as the patients' comorbidity, and smoking habits are missing in this dataset. Some prescriptions were missing due to

Table 4. Association between physician characteristics and belonging to the high prescribing group as compared to the decreasing prescribing group.

	Crude model		Adjusted model	
	OR	95% CI	OR	95% CI
Male	1.24	0.56–2.75	0.53	0.11–2.48
Birth year	0.99	0.96–1.03	0.96	0.89–1.03
Number of PHCC	1.28	1.06–1.54	1.20	0.86–1.66
Median CRP level if antibiotics (mg/L)	0.92	0.88–0.96	0.99	0.93–1.06
Negative RADT treated with antibiotics (%)	1.08	1.04–1.11	1.08	1.02–1.14
Potential bacterial diagnoses (% of index visits)	1.31	1.18–1.46	1.32	1.15–1.52

The variables are based on data for all nine years and assigned to the physician of the index visit. Crude and adjusted odds ratio (ORs) with 95% confidence intervals (95% CI). Adjusted ORs were calculated using multiple logistic regressions with a full model.
Number of PHCC – the number of primary health care centres the physician has worked at. Median CRP level if antibiotics – the median C-reactive protein level for the physicians' patients at index visits who were prescribed antibiotics. Negative RADT treated with antibiotics – the proportion of patients where rapid antigen detection test for Group A *Streptococci* was performed with negative results and still prescribed antibiotics. Potential bacterial diagnoses – acute media otitis, pharyngotonsillitis, pneumonia, and sinusitis.

being prescribed in a dose-dispensing system without connection to the electronic medical records, which mainly affects prescriptions to some elderly patients (75 years and older).

The dataset was collected prior to the introduction of telehealth medicine and before the onset of the COVID-19 pandemic, which may limit its relevance to current healthcare practices. However, concerning factors that influence the physicians' antibiotic prescribing, we believe that this study is still relevant, since the differences between prescriber groups, the choices of point-of-care use and its interpretation as well as the choice of diagnosis are not likely to be affected by telehealth services or post-pandemic healthcare.

Furthermore, the study included only 161 physicians from one region in Sweden with less than 200,000 inhabitants, thus lessening the generalizability of the results. However, these physicians who remained in the region and did not retire took care of two-thirds of all RTI visits. Also, a reduction in antibiotic prescribing has been seen in the whole country during the study years. Therefore, it would be reasonable to generalise to the rest of Sweden and to other low-prescribing countries.

A general decrease in antibiotic prescribing

The reduction in antibiotic prescribing in the study was similar throughout Sweden [7] and in other countries such as Norway [17], Finland [18], England [19] and Denmark [20] during the same period, but not in Australia [21]. Possible explanations include introducing the pneumococcal vaccination programme for children in 2009, financial incentives for reaching targets at regional and PHCC level of reduced level of antibiotic prescriptions, public awareness of the disadvantages of antibiotics, and antibiotic stewardship. The programme Strama for national antibiotic stewardship has been running since 1995 with a wide range of actions: committed work at the local and national levels, monitoring antibiotic use, surveillance of resistance, raising awareness and behavioural change [15]. Consequently, the Decreasing Prescribing Group in this study was large.

Characteristics of prescribers

Physicians with few RTI visits were more likely to belong to the Low Prescribing Group. The reason is unclear. They may have a patient population with a higher prevalence of chronic diseases and a lower incidence of acute infections. Alternatively, it might be attributed to random chance.

Physicians' age did not affect the antibiotic prescribing rate in this study. However, an earlier study from Sweden has shown that older physicians are more prone to antibiotic prescribing [22], and a similar pattern has been reported in Canada, England, Germany, and the Netherlands [11,23–25]. Since only a few physicians increased their antibiotic prescribing over time, they seem more likely to maintain their prescribing pattern with increasing age. Perhaps the higher prescribing rate seen among older physicians in other studies reflects a higher general prescribing rate when the physicians were younger.

Locum physicians have sometimes been identified as high prescribers [26]. In this study, the locums belong to the exclusion group, which had the same antibiotic prescribing rate as the included physicians. Some studies have reported more high prescribers among physicians trained abroad [23,24]. Unfortunately, this study lacks information about the education country.

Point-of-care tests

Although significantly different at the group level, the use of CRP test was not significantly different at the physician level amongst the prescriber groups. The use of RADT was more common in the High Prescribing Group than in the other prescriber groups both at group level and physician level. Also, the High Prescribing Group used antibiotics at lower CRP levels and more often when RADT was negative. It is unclear whether point-of-care tests decrease or increase antibiotic prescribing. In this study, the use of CRP testing was increasing while the antibiotic prescribing was decreasing. A similar pattern was seen in a Danish study of primary care [27]. A Cochrane review shows that CRP testing for acute respiratory tract infections reduces antibiotic prescribing [28]. Other studies show that RADT testing for GAS increases antibiotic prescribing [6,29,30].

It can be argued that the lower median CRP levels and the higher incidence of negative RADT observed in the High Prescribing Group when prescribing antibiotics may represent circular evidence. Assuming the patient populations are similar, this will follow if more antibiotics are prescribed. However, focusing on interpreting point-of-care results could be a way forward in antibiotic stewardship.

Choice of diagnoses

In a Swedish context, the diagnosis 'Upper RTI' is considered to be of viral origin. Physicians in the Low Prescribing Group were more likely to diagnose upper RTI, while physicians in the High Prescribing Group were more likely to register a diagnosis with potential bacterial aetiology. The same pattern is seen in several other studies where the proportion of potential bacterial diagnoses corresponds to the antibiotic prescribing rate [11,31,32]. The assumption is that an infection is assigned a potential bacterial diagnosis to justify the use of antibiotics.

Follow-up

Earlier studies have reported a rate of 27–38% of return visits within a month. Some have shown a higher rate of return visits if antibiotics were prescribed at the index visit, and others have shown the opposite [33–35]. The rate of return visits was generally lower (14%) in the current study. The low rate of return visits is probably due to generally fewer consultations per inhabitant. There is a small statistical difference in return visits amongst the prescriber groups, but the effect size is small, and the difference is clinically irrelevant. When comparing at the physician level, the only difference was a lower return visit rate in the Decreasing Prescribing Group compared to the High Prescribing Group.

The proportion of a second antibiotic prescription within 30 days was statistically significant between the prescriber groups, but again the effect size was small, and the difference lacks clinical significance. When comparing at the physician level no significance was seen.

Other explanations

Generally, the physician is considered solely responsible for prescribing antibiotics, but other factors such as the impact of the PHCCs and patients' expectations are relevant [11,13,36]. These factors have not been explored in this study.

Qualitative studies have identified several potential factors. A study of sore throat identified different strategies for physicians to cope with uncertainty: adherence to guidelines; clinical picture and CRP; expanded control; and unstructured examination [37]. In a study of lower RTI, physicians mentioned that fear of consequences was a reason for antibiotics [38]. In a recent study on acute sinusitis, physicians mentioned sympathy with the patient, contextual factors such as Fridays with limited possibility to follow-up, and the patient's appearance and level of pain [39].

Physicians' choice to prescribe antibiotics may be motivated by special circumstances (no possibility of follow-up; previous severe infections; close relation to an immunocompromised patient; or concurrent severe diseases). Perhaps physicians in the High Prescribing Group were more likely to identify special circumstances that motivated them to prescribe antibiotics.

Implications

The study highlights potential factors to address regarding high antibiotic prescribers, such as the tendency to overuse point-of-care tests and the quality of the interpretation of tests. Furthermore, the result emphasises the importance of correct diagnosis to maintain high quality in antibiotic prescribing. The results could be useful in quality improvement in primary care, focusing on information, continuous medical education on indications, usefulness and interpretation of the point-of-care tests.

Conclusion

The use and interpretation of point-of-care testing were different amongst the prescriber groups. The High Prescribing Group did more CRP testing, prescribed antibiotics at lower CRP levels, performed more RADT for GAS, prescribed antibiotics more often although negative RADT, and were more prone to register a diagnosis with potential bacterial aetiology than the Low Prescribing Group. The Decreasing Prescribing Group was in between the High Prescribing Group and the Low Prescribing Group regarding these variables. There was no clinically relevant difference in the proportions of return visits and new prescriptions of antibiotics within 30 days in the three prescriber groups. According to our results, focusing on the use and interpretation of point-of-care tests is a possible way to improve antibiotic stewardship.

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Ethical approval

Confidentiality of the patients was ensured by one-way encrypted identification numbers. Ethical approval was obtained from the Regional Ethical Review Board in Linköping, Sweden (Dnr 2014/121-31).

Author contributions

OC and KH initiated the study. OC managed and validated the KIDPC dataset. OC carried out the analysis of the data and drafted the manuscript, which was evaluated by KH, MT, and KE. All authors critically revised and approved the final manuscript.

Disclosure statement

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Data availability statement

The datasets used and analysed in the current study are available with the corresponding author upon reasonable request.

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