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Quality in antibiotic prescribing in primary care. Current practice, relation to guidelines and antimicrobial resistance.

Tyrstrup, Mia

2017

Link to publication

Citation for published version (APA):
Tyrstrup, M. (2017). *Quality in antibiotic prescribing in primary care. Current practice, relation to guidelines and antimicrobial resistance.* [Doctoral Thesis (compilation), Department of Clinical Sciences, Malmö]. Lund University: Faculty of Medicine.

Total number of authors:
1

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Quality in antibiotic prescribing in primary care

Current practice, relation to guidelines and antimicrobial resistance

MIA TYRSTRUP
GENERAL PRACTICE/ FAMILY MEDICINE | LUND UNIVERSITY

Quality in antibiotic prescribing in primary care

Quality in antibiotic prescribing in primary care

Current practice, relation to guidelines and antimicrobial resistance

Mia Tyrstrup

DOCTORAL DISSERTATION
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To be defended on October 20th 2017, 9.00 am..

Faculty opponent
Hans Fredlund

Organization
LUND UNIVERSITY

Author(s): Mia Tyrstrup

DOCTORAL DISSERTATION

Date of issue: 20 October 2017

Sponsoring organization

Title and subtitle: Quality in antibiotic prescribing in primary care. Current practice, relation to guidelines and antimicrobial resistance.

Background: Bacterial resistance is a major and growing global issue highly prioritised by the World Health Organization (WHO). The use of antimicrobial agents is known to promote bacterial resistance. In Sweden, as well as other European countries, the majority of antibiotics are prescribed in primary care. An excessive use of antibiotics is no longer acceptable and we must find ways to reduce our consumption.

Objectives: The aim of the thesis was to analyse aspects of quality in antibiotic prescribing for common infections in primary care with regards to current practice, adherence to national guidelines and antimicrobial resistance.

Methods: In paper I, Sweden's largest register in primary health care for diagnosis-linked antibiotic prescription data was used; the Primary Care Record of Infections (PRIS) with 700,000 listed patients was analysed to describe current practice and adherence to guidelines during the years 2008-2013. European Antibiotic Prescribing Quality Indicators (APQI) for primary care was evaluated in paper II using register data from Belgium, the Netherlands and Sweden. In order to map bacterial resistance in primary health care, 340 nasopharyngeal cultures were gathered from children seeking their Primary Health Care Centre (PHCC) in the region of Scania due to respiratory tract infections. The cultures were analysed in paper III and related to a parental questionnaire containing information about the children's previous antibiotic use and other factors. In paper IV, we analysed 29 interviews with Swedish GPs to explore how they describe the management of respiratory tract infections in relation to national guidelines and we evaluated possible barriers to adherence.

Results: We found increased adherence to national guidelines regarding respiratory tract infections in primary care, as a result of reductions in consultations and antibiotic prescription rates. Quality assessment using European disease-specific APQIs was feasible and could identify improvement areas, but their interpretation requires accounting for consultation incidences and national guidelines.Children in Swedish primary care had a low level of Pneumococci with reduced sensitivity to penicillin (PNSP) and phenoxymethylpenicillin is valid as empirical treatment if antibiotics are required. Antibiotic treatment conducted four weeks previously was associated with bacterial resistance, OR=3.08, 95% CI (1.13-8.42).We found that if guidelines are not compatible with the GP's existing norms the adherence might be low regardless of the presence of all the attributes found to be of importance for adherence to guidelines.

Conclusions: Trends show a continuous decrease in antibiotic use in primary care, but large differences in prescribing between practices indicate continuing overuse of antibiotics. Regular monitoring and feedback to prescribers are essential in order to further improve antibiotic prescribing.Comparing quality in antibiotic prescribing between nations was made complex due to differences in medical health care systems, diagnoses registration, cultural differences and incompleteness of register data and needs further attention. By comparing antibiotic prescribing data internationally, identification of factors influencing prescription rates becomes evident. GPs' persisting conceptions about the diagnostic procedures and treatment are important to address when creating guidelines, as they could otherwise act as a barrier to adherence.

Keywords antibiotic prescribing, antimicrobial resistance, primary health care, respiratory tract infections, guideline adherence, antibiotic prescribing quality indicators

Classification system and/or index terms (if any)

Supplementary bibliographical information

Language: English

ISSN ISSN 1652-8220

ISBN 978-91-7619-518-5

Recipient's notes

Number of pages

Price

Security classification

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Quality in antibiotic prescribing in primary care

Current practice, relation to guidelines and antimicrobial resistance

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ISBN 978-91-7619-518-5
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2017

To Léon, César and Élise

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Abstract

Background: Bacterial resistance is a major and growing global issue highly prioritised by the World Health Organization (WHO). The use of antimicrobial agents is known to promote bacterial resistance. In Sweden, as well as other European countries, the majority of antibiotics are prescribed in primary care. An excessive use of antibiotics is no longer acceptable and we must find ways to reduce our consumption.

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Results: We found increased adherence to national guidelines regarding respiratory tract infections in primary care, as a result of reductions in consultations and antibiotic prescription rates. For urinary tract and skin and soft tissue infections, the antibiotic prescribing was unchanged.

Quality assessment using European disease-specific APQIs was feasible and could identify improvement areas, but their interpretation requires accounting for consultation incidences and national guidelines.

Children in Swedish primary care had a low level of Pneumococci with reduced sensitivity to penicillin (PNSP) and phenoxymethylpenicillin is valid as empirical treatment if antibiotics are required. Antibiotic treatment conducted four weeks previously was associated with bacterial resistance, OR=3.08, 95% CI (1.13-8.42).

We found that if guidelines are not compatible with the GP's existing norms the adherence might be low regardless of the presence of all the attributes found to be of importance for adherence to guidelines.

Conclusions: Trends show a continuous decrease in antibiotic use in primary care, but large differences in prescribing between practices indicate continuing overuse of antibiotics. Regular monitoring and feedback to prescribers are essential in order to further improve antibiotic prescribing.

Comparing quality in antibiotic prescribing between nations was complex due to differences in medical health care systems, diagnoses registration, cultural differences and incompleteness of register data and needs further attention. By comparing antibiotic prescribing data internationally, identification of factors influencing prescription rates becomes evident.

If antibiotics are deemed necessary for a respiratory tract infection, phenoxymethylpenicillin can be used in primary care, as levels of resistant pneumococci are low. Resistance levels measured in the local microbiological laboratory may not always be transferable to a primary care population.

GPs' persisting conceptions about the diagnostic procedures and treatment are important to address when creating guidelines, as they could otherwise act as a barrier to adherence.

Abbreviations

AOM	Acute Otitis Media
APQI	Antibiotic Prescribing Quality Indicator
BLNAR	Beta-lactamase Negative Ampicillin Resistant *H.influenzae*
CI	Confidence Interval
CRP	C-Reactive Protein
DDD	Defined Daily Dose
DID	Defined Daily Dose per 1000 inhabitants per day
ESAC	European Surveillance of Antimicrobial Consumption
GAS	Group A beta-haemolytic Streptococci
GP	General Practitioner
LRTIs	Lower Respiratory Tract Infections
MIC	Minimum Inhibitory Concentration
NP	Nasopharynx
Penicillin V	Phenoxymethylpenicillin
PHCC	Primary Health Care Centre
PID	Number of packages per 1000 inhabitants per day
PNSP	Penicillin Non-Susceptible Pneumococci
PRIS	Primary Care Record of Infections in Sweden
PY	Patient Years
RADT	Rapid Antigen Detection Test
RTI	Respiratory Tract Infection
SST	Skin and Soft Tissue infection
Strama	The Swedish Strategic programme against antibiotic resistance
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection

Original papers

This thesis is based on the following papers referred to in the text by their Roman numerals:

I. Tyrstrup M, Beckman A, Mölstad S, Engström S, Lannering C, Melander E, Hedin K: Reduction in antibiotic prescribing for respiratory tract infections in Swedish primary care. A retrospective study of electronic patient records. *BMC Infectious Diseases*. 2016, 16:709

II. Tyrstrup M, van der Velden A, Engstrom S, Goderis G, Mölstad S, Verheij T, Coenen S, Adriaenssens N: Antibiotic prescribing in relation to diagnosis and consultation rates in Belgium, the Netherlands and Sweden: use of European quality indicators. *Scandinavian Journal of Primary Health Care.* 2017, 35:1

III. Tyrstrup M, Melander E, Hedin K, Beckman A, Mölstad S: Children with respiratory tract infections in Swedish primary care. Prevalence of antibiotic resistance in common respiratory pathogens and relation to antibiotic consumption. *BMC Infectious Diseases.* 2017, 17:603

IV. Tyrstrup M, André M, Brorsson A, Gröndal H, Strandberg E-L, Hedin K: Stated adherence to guidelines in relation to guideline characteristics. Analysis of guidelines and of interviews with General Practitioners in Sweden. *BMC Family Practice (submitted)*

Overview of thesis

Table 1.
Overview of thesis

Paper	Purpose	Methods	Results	Conclusions
I	Identify trends in consultation rates and antibiotic prescribing in Swedish primary care over time, particularly for RTIs with regard to adherence to national guidelines.	Retrospective register study. Analysis of diagnosis linked prescription data from the Primary Care Record of Infections (PRIS), 2008-2013.	Reduced consultaion and prescribing rates for RTIs. Improved adherence to guidelines for AOM and tonsillitis.	Decrease in antibiotic prescribing for RTIs in primary care. Support the importance of guidelines for correct antibiotic prescribing.
II	Evaluate European Antibiotic Prescribing Quality indicators (APQIs).	Retrospective register study comparing APQIs by using diagnosis linked prescription data for primary care from Belgium, the Netherlands and Sweden.	The APQI can be used to identify improvement areas but needs to take into account consultation incidence and national guidelines for each country.	The APQIs were useful to some extent but need further improvments.
III	Measure bacterial resistance in children in primary care and its correlation to antibiotic use.	Prospective study, analysis of nasopharyngeal cultures from children age 0-10 with symptoms of RTIs and evaluation of parental questionnaires.	340 cultures with low levels of PNSP (6%). Associaltion between previous antibiotic use and resistance.	Low levels of bacterial resistance. Penicillin V still valid as empirical treatment in RTIs if antibiotic deemed necessary.
IV	Analyse GPs' stated management and adherence to guidelines for LRTIs, AOM and tonsillitis and explore how this relates to guideline characteristics.	Qualitative study analysing guideline characteristics and semi-structured interviews of 29 GPs.	The most important guideline characteristic was the conformity to existing norms correlating to GPs' persisting concepts	Taking GPs' persisting concepts into consideration when creating national guidelines is important as they can otherwise act as barriers to adherence.

Introduction

Antimicrobial resistance is predicted to be the major cause of death by 2050 worldwide [1]. Global efforts are being made to curb the problem. High antibiotic use is related to high levels of antimicrobial resistance [2]. The Swedish government has set up goals to limit antibiotic consumption [3]. Primary care accounts for about two-thirds of the antibiotic prescribing in Sweden. A considerable reduction in antibiotic prescribing has been seen in Sweden over the last 25 years, but there are still signs of overconsumption for self-limiting common infections [4]. With this thesis, we attempt to fill in some of the blanks necessary to move forward towards a more reasonable antibiotic use.

In order to be more specific as to how we could improve antibiotic use further, we need to study how doctors are prescribing today. By analysing diagnosis-linked prescription data we can be more specific in our goals. **(Paper I)**

There is a need for valid parameters that can be followed over time and used to compare quality in antibiotic prescribing between prescribers as well as on national and international levels. Evaluation of such quality indicators is important in order to develop future tools to measure and compare antibiotic prescribing. **(Paper II)**

Monitoring resistance levels in primary care populations is important to ensure the empirical antibiotic treatment recommended by guidelines is correct. **(Paper III)**

National guidelines for diagnoses and treatment of common infections in primary care are not fully adhered to. Further analysis as to how we can tackle this problem is needed. **(Paper IV)**

Background

Antibiotics

The discovery of antibiotics

The word "antibiotics" comes from the Greek words; anti = against and bios = life. Antibiotics are substances produced by living organisms in order to keep other organisms away. For example, mould produces penicillin to keep away bacteria. The mould that grew on Alexander Fleming's agar plates in 1928 was developed into a life-saving treatment and penicillin was introduced clinically by Florey and Chain in the 1940s. Several other antibiotics have been developed and used readily in medical care since then. (Figure 1) Antibiotics excerpt their effects on bacteria by affecting the cell wall build-up (penicillins, cephalosporins), disrupt the protein synthesis (tetracycline, aminoglycoside, macrolide and linkosamines), affect membrane permeability (polymyxin E), disrupt DNA-synthesis (quinolones, metronidazole) or disrupt metabolism (trimethoprim, sulphonamide). Today antibiotics are some of the most important drugs in medicine. Their use is not only to treat invasive infections, but many surgical interventions, organ transplantations and cancer treatments are dependent on their effectiveness. Since the 1980s very few new antibiotics have been developed, which is worrying due to the rising problem of bacterial resistance.

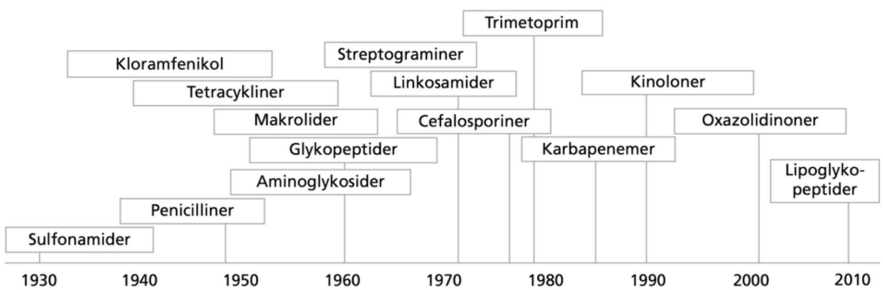

Figure 1.
Development of new antibiotic classes since the 1930's. (source: www.lakemedelsboken@mpa.se)

Bacterial resistance

Very soon after antibiotics were introduced in clinical use microbial resistance also developed. In Alexander Fleming's Nobel lecture from 1945, where he had already presented rules for penicillin treatment, he pointed out the importance of acquired resistance even though there was little of it at the time [5]. Clinically significant resistance appears in periods from months to years to a newly developed antibiotic [6,7].

Even though the phenomenon was known long before, the problem did not start to be recognised until the 1970s when the first resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* were detected. The WHO has forecast that antimicrobial resistance will be the major cause of death in 2050, causing 10 million deaths worldwide, while cancer will cause 8.2 million and car accidents 1.2 million deaths [1] respectively. In Sweden alone, the antimicrobial resistance is estimated to cost an extra five billion SEK 2015-2024 [8].

Antibiotic use in the community (veterinary, agricultural and human medicine) as well as the individual consumption matter in the development of antimicrobial resistance. The antibiotic exerts a selection pressure so that the susceptible bacteria are eliminated and opportunities are given for the resistant sub-populations to grow. Studies have shown that high antibiotic consumption is associated with high antimicrobial resistance, both on a community and individual level [2,9–12].

The use of antibiotics in animal husbandry for growth promotion was prohibited in 1986 in Sweden and in the EU in 2006. In 2015, 60 tonnes of antibiotics were used in human medicine and 10 tonnes in veterinary medicine in Sweden [13]. While the opposite relation is true in many other countries, where non-medical arenas use up to ten-times the amount antibiotics consumed in human medicine [14].

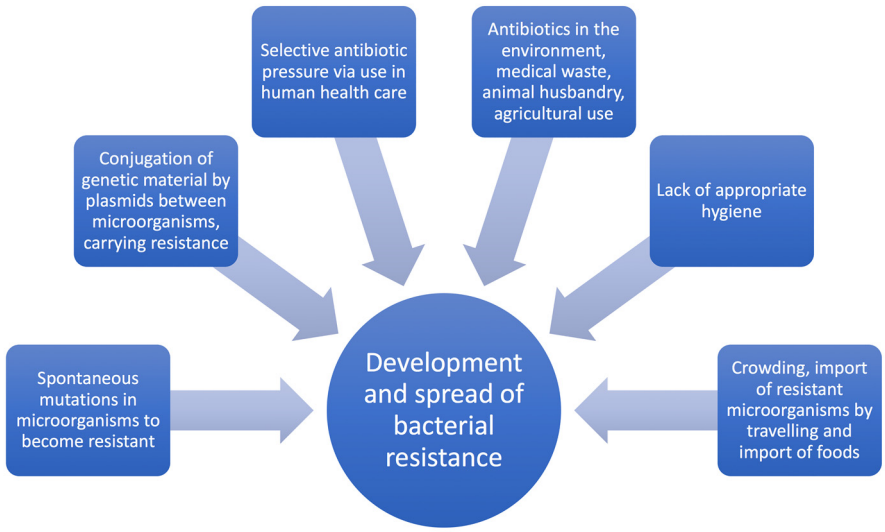

Figure 2.
Factors affecting the development and spread of bacterial resistance.

Resistance mechanisms

Bacterial resistance is acquired by spontaneous mutations or by horizontal gene transfer such as conjugation of genetic material via plasmids from other resistant bacteria. The genetic materials are coding for one or more of the following resistance mechanisms; a) production of enzymes that destroy the antibiotic such as Beta lactamase, b) a change in the binding site for the antibiotic so that it cannot attach to the bacteria, c) increased efflux of antibiotic out of the bacteria by special pumps or d) activation of alternative metabolic pathways [15].

Monitoring of bacterial resistance

The development of antimicrobial resistance in primary care populations over time has been poorly studied. In Sweden, carriage rates of *Streptococcus pneumoniae,* commonly referred to as pneumococci and other nasopharyngeal flora, have been followed in particular projects (South Swedish Pneumococcal Project) [16] and measured in healthy child care groups [17]. The microbiological laboratories in Sweden collect 100 consecutive cultures of selected species every year to monitor resistance levels. These cultures originate from a mixed population including patients in hospital care, hospital outpatient clinics and patients in primary care. The distribution between the groups is not monitored. Furthermore, the history of

the patients or reasons for sampling is not known so whether these cultures are representative of primary care populations is not established.

The Public Health Agency is now working on a new surveillance system, called Svebar, to monitor bacterial resistance and collaborate nationally and regionally in Sweden in order to give early warning and adequate support in case of a larger outbreak. Since the outbreak of resistant pneumococci in the late 1980's the levels of PNSP (MIC≥0,12 mg/L) in the microbiological laboratories have been low (3-5%), compared to international data [16,18] Studies on primary care populations are required to evaluate the level of antimicrobial resistance and evaluate the usefulness of current recommendations for empirical antibiotic treatment for common infections.

Prevention of further spread and development of resistance

Preventing further spread and development of resistance requires optimisation of antibiotic prescribing. Furthermore, it requires prevention of disease spreading by means of correct hygiene and vaccination programs.

In Sweden, a rise in *Streptococcus pneumoniae* with reduced sensitivity to penicillin (PNSP) was noted in the late 1980's. This was the starting point for more action being taken to prevent further development of resistance. The Swedish strategic program against antibiotic resistance (Strama) was formed in 1995. Strama co-operates with the Swedish government and the Public Health Agency and has a national and several regional groups working towards the main goal to preserve the effectiveness of antibiotics. Strama has organised campaigns to increase public knowledge about antibiotics and resistance and conducted regular meetings and education for medical personnel, both in primary and secondary care, as well as in dental and veterinary care. An important part of Strama's work has been to implement and promote national guidelines for diagnosis and treatment of common infections in order to optimise the antibiotic use in both primary and secondary care.

A national cooperation regarding antimicrobial resistance was started in 2012 where the Public Health Agency, the agricultural authorities and 23 other Swedish authorities participated. In 2010 the government set up a national quality goal to reduce the number of antibiotic prescriptions to 250 prescriptions per 1000 inhabitants per year by 2014. This goal was not reached, but a continuing decrease in antibiotic prescribing has been seen since and in 2016 the figure was 318 prescriptions per 1000 inhabitants [4].

The importance of correct hygiene to prevent infections was discovered by Semmelweis in the 19th century and plays an important role in today's prevention

against the spread of resistant bacteria. Several intervention studies promoting correct hand hygiene have achieved reductions in the prevalence of resistant bacteria [19]. The Public Health Agency of Sweden acts to limit health care associated infections from emerging and spreading by promoting improved hand hygiene within the health and social care services [20].

Furthermore, exploring evidence supporting alternative treatments for infections, such as probiotics [21,22], fecal microbiota transplantation [23], bacteriofaghs [24] and immune regulating therapy [25] are interesting ways forward to decrease the use of antibiotics and reduce the development of resistance.

Vaccination effects

Vaccination against *H.influenzae* in Sweden was introduced in 1993 and since then the invasive *H.influenzae* causing epiglottitis and meningitis has been substantially reduced. There has been an increase in colonisation of *Staphylococcus aureus* and a shift towards a non-capsular type of *H.influenzae*, which is less virulent, but can still cause AOM and other URTIs [26].

The first pneumococcal vaccination was introduced nationally in the Swedish general vaccination programme in 2009 and covered seven serotypes of *S.pneumoniae*. Today, the current vaccination contains 13 serotypes and the vaccination coverage in Sweden is 97.5% [27]. Since the introduction of the vaccine there has been a reduction of pneumococcal carriage and a shift towards non-vaccine serotypes [28–31], also in non-vaccinated populations [32]. Some studies report an increase in *H.influenzae* carriage [33,34] and others no change [35] in carriage rate of *H.influenzae* or *Moraxella Catarrhalis* after introduction of pneumococcal vaccine.

Vaccination against *S.pneumoniae* has reduced the number of serious infections such as pneumonia in small children <2 years of age [36]. Although the 2014 Cochrane review could only find modest beneficial effects on AOM of pneumococcal vaccine, later studies have shown a reduced incidence of AOM after vaccination [29,37]. In Sweden, reduced hospitalisation for sinusitis and pneumonia for small children has been noted after the introduction of pneumococcal vaccination [38].

Ecological aspects

The extensive use of antibiotics also results in environmental releases from both the production process and in the sewage. Even in low concentrations, antibiotics

promote selection of resistant bacteria in the environment and increases the prevalence of elements for horizontal gene transfer [39,40].

The human body contains different bacterial niches, for example on the skin, gut, vagina and in the nasopharynx. The extents to which the use of antibiotics has affected the human microbiome and changed the balance of the human body's own ecosystem is not fully known. Facts have been discovered which indicate that antibiotic use affects the development of diseases such as gastroesophageal reflux (GERD) asthma, allergies and obesity [41]. Presence of resistance genes in the microbiota of the gut remained for at least four years after a short term treatment of clarytromycine and metronidazole [42]. Evidence that we are more susceptible to new infections after an antibiotic treatment has been presented [9].

Furthermore, adverse reactions to antibiotics are common in the form of gastrointestinal side effects, rashes, nausea, and candida infections. These negative effects of antibiotic treatments are important to discuss with the patient in order for the individual to make an informed consent to treatment.

Infections in primary care

In Sweden about 30% of the consultations in primary care concern infections [43]. Among the five most common diagnoses in primary care, three were infection related, of which the most common was unspecific upper respiratory tract infection, including the common cold [44]. In Sweden, the consultation rates for infections in primary care decreased considerably in the beginning of the 20th century (39% between 2000 and 2005) [45,46]. About 60% of the consultations for infections regarded the respiratory tract, 15% concerned urinary tract and 12% skin and soft tissue in a Swedish primary care population in 2013 [43].

Infections presented in primary care range from harmless colds to severe and sometimes life-threatening infections such as pneumonia, sepsis and meningitis. The GP has to differentiate between what needs to be treated with antibiotics and what does not, or need to be referred to secondary care, often during only a few minutes long consultation. Life threatening, serious infections are rare in primary care. That is why GPs cannot use clinical guidelines based on research performed on highly selected populations seen in secondary care. Diagnostic work in primary care means to suspect the common, but keep in mind and exclude the unusual diagnoses. Treating everyone with a sore throat to prevent extremely rare complications is not realistic when taking into account side effects of drugs, ecological aspects of antimicrobial resistance and capacity [47].

Systematic reviews based on primary care research are helping to conclude the best evidence for when treatment with antibiotics are beneficial (pneumonia in children) and when not (AOM ages 1-12 years unless complicating factors, cough, common cold) [48–51]. Monitoring of complications of common infections is essential to prevent under-treatment. During the years 1995-2004, when a large reduction in outpatients' antibiotic use was seen in Sweden, the hospital admission rate for acute mastoiditis, sinusitis and peritonsillar abscess was stable [52]. Furthermore, there was a large retrospective study which showed that the number of acute mastoiditis did not increase after the introduction of a more restricted antibiotic use for AOM [53]. A protocol regarding how to register antibiotic use as well as monitoring complications to RTIs has been produced by The Public Health Agency of Sweden (the MIRA project) in 2014 but has not yet been practised on a regular basis [54].

Primary care in Sweden

Health care systems with a strong primary care orientation have proven to be cost effective and associated with higher patient satisfaction [55,56]. In Sweden, the health care system relies on a well-functioning primary care, which intends to provide equal care to all citizens, be readily accessible and at the same time produce high-quality care in many medical fields as well as provide continuous care to chronically ill patients.

Primary care has many challenges, including finding enough resources. Only 20% of the total health care budget in Sweden is spent on primary care and about 20% of the doctors work in the approximately 1100 primary health care centres (PHCCs) around the country [57]. The structure of the primary care system, as it is known today, started to develop in the 1970s [58,59]. Since then several new reforms to improve the system have been implemented with mixed results. Sweden is divided into 21 county councils and each region organises the primary care service according to their local decisions and finances. Since 2010 patients can register with any public or private provider accredited by the local county council and registration based on latest visit or shortest geographical distance is practised in most county councils for individuals who do not make an active choice of provider. Irrespective of registration, however, primary care has no formal gate-keeping role in the county councils and patients are free to contact specialists directly [57]. Primary care is responsible for the care of all ages, except for babies less than six months old (who are recommended to consult a paediatrician). In Sweden, the most common way to present to primary care is to consult with a nurse first who evaluates the problem and then decides either to book a doctor's appointment or to give self-advice. The selection of patients, via nurse triage, seems effective to lower the number of doctors' consultations and

Sweden has lower consultation incidences for infections than other European countries [60].

Furthermore, clinical studies on Swedish primary care patients are few. The existing national guidelines regarding diagnosis and treatment are mostly based on RCT-studies performed in England and the Netherlands. Research based on primary care populations is important for the development of correct clinic guidelines based on evidence. The role of primary care is extremely important as it is often the patients' first meeting with the health care system and it is where important decisions are being made regarding the patients' future care.

Antibiotic prescribing

In Sweden 10% of the antibiotics are consumed in hospital care. The other 90% is prescribed in outpatient care and divided between primary care (61%), hospital outpatients care (23%), specialist clinics outside the hospitals (5%), dentistry (7%) and others (4%) The figures presented in Figure 3 are based on data from the Medical database in the region of Scania, and the figures are similar for the whole of Sweden [4].

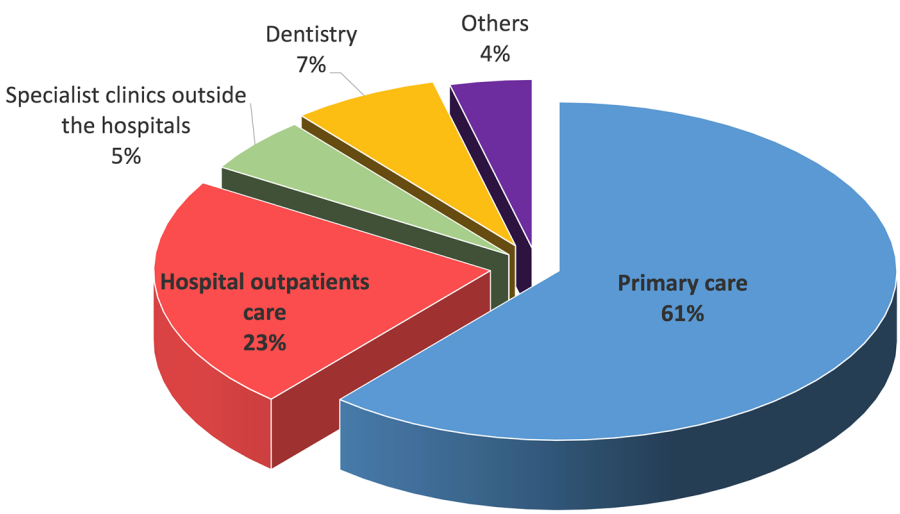

Figure 3.
Distribution of antibiotic prescribing in outpatient care in the region of Scania. (data source: The medical database, region of Scania, 2017)

Although the total outpatient antibiotic prescription rate in Sweden has decreased by 42% in the last 20 years [4], the use of antibiotics continues to increase on a global scale. The global antibiotic consumption rose by 40% between 2000 and 2010 [61]. In most European countries the antibiotic use has increased in the period 1997-2009 [62].

In Sweden, the antibiotic use in outpatients peaked in 1993 and has since decreased to a national average of 318 prescriptions per 1000 inhabitants per year in 2016 [4]. It is the antibiotic prescribing for children 0-4 years of age that has decreased the most in Sweden; approximately 73% since 1992. Today it is the population >65 years of age who are prescribed the most antibiotics [4].

There are still large variations in antibiotic prescribing between different regions in Sweden, ranging from 345 prescriptions per 1000 inhabitants per year in the region of Stockholm and 252 in the region of Västerbotten in 2016 [4]. These differences are difficult to explain and they indicate that overprescribing of antibiotics still exists. Further investigations to correlate the prescriptions to diagnoses are important in order to direct interventions to improve prescribing in primary care. The PRIS register is the first large-scale register with diagnosis linked antibiotic prescriptions in Sweden. Analysis of diagnosis linked prescription data is important for the future work towards more prudent antibiotic use.

The Swedish HALT project (HALT= Healthcare associated infections and antimicrobial use in long-term care facilities) is an annual point prevalence survey that aims to support prevention of health care associated infections and improve the use of antibiotics in assisted living facilities. The HALT project collects diagnosis linked prescription data from long-term care facilities.

Quality in antibiotic prescribing

Quality in antibiotic prescribing is to use the most suitable antibiotic at the right time, with the right dose for the right length of time. To preserve the valuable effects of antibiotics must be the ultimate goal.

The most suitable antibiotic, according to evidence-based guidelines and knowledge of local resistance patterns must be chosen.

At the right time, meaning only in situations where there is evidence for antibiotics to be effective, and where we believe the available evidence supports that benefits outweigh the adverse effects of antibiotic treatment.

With the right dose, meaning using the correct dose and number of doses per day to maintain proper time over MIC to be effective.

Right duration of treatment, meaning not treating for longer time than necessary. To reduce side effects on the normal bacterial flora and the selection of potential resistant strains of bacteria.

To help us maintain these quality aspects, national guidelines for diagnoses and treatment for common infections have been developed.

Quality is not buying antibiotics online or over the counter in pharmacies without a prescription. Quality in antibiotic prescribing requires a physician to take responsibility for the prescription and perform follow-up of the treatment, if appropriate.

Furthermore, quality is informing the patient about potential benefits and harms with antibiotic treatment in order to make an as good informed consent to the treatment as possible [63–65]. Shared decision making between physician and patient has proven to reduce antibiotic consumption at least on a short-term basis [66].

The concept that an antibiotic course should always be completed to minimise resistance is no longer valid due to lack of evidence [67]. In contrast, there is evidence that the risk of acquiring resistant bacteria increases with the duration of the antibiotic course [68,69].

Adherence to guidelines

Studies have shown that adherence to guidelines is not satisfactory [70,71]. Guideline adherence has been shown to be better among younger GPs compared to older and to locums [72]. Studies exploring the reasons why doctors do not follow guidelines have described the implementation process of guidelines to occur in the context of conflicting pressures for clinical autonomy and professional standardisation and quality improvement [73]. Controversial or vague guidelines, and guidelines demanding change in current practice and lacking evidence base have proven to be less adhered to [74]. Other perceived barriers are lack of applicability of recommendations to individual patients [75].

Interviews with Swedish GPs regarding national guidelines of tonsillitis showed that non-adherent GPs had significant knowledge gaps and had not discussed the guidelines with their primary care team [76]. The doctors relied more on their senses than on the Rapid Antigen Detection Test for GAS (RADTs) and often overruled a negative test result and treated with antibiotics if their clinical gaze indicated so [77], while the opposite was true about the use of C-reactive protein

(CRP). CRP was often used to differentiate between bacterial and viral origin of an infection and the result of CRP was regarded as very trustworthy despite lacking evidence [77–80]. However, only a few studies in primary care have looked at the specific characteristics of the guideline in connection with the GPs' adherence.

How do we measure quality in antibiotic prescribing?

On a European level, the European Centre for Disease Prevention and Control (ECDC) website monitors the Defined Daily Doses per 1000 inhabitants per day (DID) for 28 countries in Europe. (Figure 4) They also monitor consumption of antimicrobials expressed as number of packages per 1000 inhabitants per day (PID). In 2012 the Netherlands had the lowest consumption measured in DID per 1000 inhabitants per day and Sweden had the lowest PID per 1000 inhabitants per day [81]. The difference is due to the longer treatments and higher doses for some infections in Sweden. It was suggested that PID was the most appropriate measure of antibiotic consumption in primary care since the number of Defined Daily Doses (DDD) per package varies between countries and also over time [82,83].

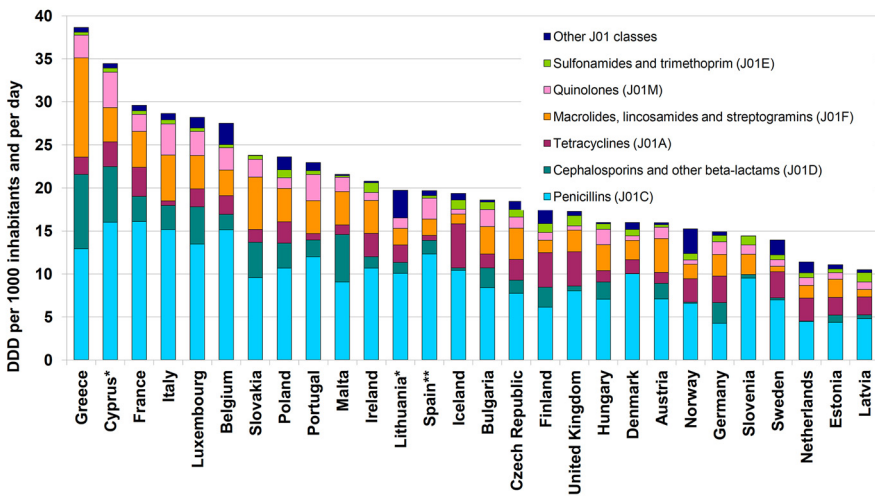

Figure 4.
Consumption of antibiotics for systemic use in the community, divided into main antibiotic classes, in 28 European countries 2009. (Data source: www.ecdc.europa.eu)

Another initiative to measure and compare quality in antibiotic prescribing internationally was the Happy Audit where GPs from six different countries registered the management of patients consulting for RTIs in primary care [84].

The risk of selection bias with only highly motivated GPs and correctly managed patients to be registered carry a risk of underestimating the problem. Furthermore, the European Surveillance of Antimicrobial consumption (ESAC) Network developed a set of Antibiotic Prescribing Quality Indicators (APQIs) in order to compare diagnosis linked prescription data between countries [62]. However, a thorough evaluation of the APQIs was required before further use.

When comparing figures of antibiotic prescription rates it is important to take into account the consultation incidence for each diagnosis, because a low consultation incidence with a high prescribing percentage can equal a high consultation incidence with a low prescribing percentage in the total amount of prescriptions.

In Sweden, the local Strama network visits each PHCC in the region to present statistics on number of prescriptions per 1000 inhabitants per year per PHCC and choice of antibiotic subgroup prescribed. Comparison to other nearby PHCCs and national figures are reflected upon. The prescription data is provided by the national pharmacy (Apoteks service AB), based on the number of prescriptions the patients have collected at the pharmacies. Furthermore, in some counties, GPs have the opportunity to extract some limited data, on a yearly basis, regarding their own antibiotic prescribing from the Swedish eHealth Agency website [85]. In a few counties, diagnosis linked prescription data are available for the local Strama network for each PHCC.

The government has set up a national goal of 250 antibiotic prescriptions per 1000 patients per year by the year 2014. In 2016 this number was 318. Most regions in Sweden also have their local yearly quality goals regarding number of prescriptions per inhabitant per year and percentage recommended antibiotic for certain diagnoses.

Via the government's initiative, The Public Health Agency of Sweden has outlined a protocol (the MIRA program) on how diagnosis linked prescription data in primary care can be monitored and what factors need certain consideration when interpreting these data [54]. Unfortunately, diagnosis linked prescription data is not available to all 21 regions of Sweden. However, the Primary Care Record of Infections (PRIS), which was the largest diagnosis-linked register for antibiotic prescriptions, provided important data used for the analysis in **Paper 1.** Data collecting to the PRIS database was closed in 2014.

Quality in prescribing of antibiotics also means not under-prescribing. Monitoring admissions to hospitals for common complications to RTIs is a way to evaluate under-prescribing. As mentioned earlier, a retrospective analysis of patient records for mastoiditis was performed in Sweden and no increase in incidence was found after the introduction of more restrictive guidelines for treatment of AOM [53] and

during the years 1995-2004, when antibiotic use decreased substantially in Swedish primary care, these complications remained stable [52].

Factors influencing antibiotic consumption

Patients' antibiotic use is in most cases the result of the following decision-making steps. First, the patient decides to present to primary care: **consultation decision**. Determinants of this step are the patients' knowledge about self-care and when to consult professional health care [86]. Furthermore, factors such as availability of health care, nurse triage, fee-for service to see a doctor, and requirement for sick-notes as well as cultural aspects play a role in the consultation decision [87,88].

Second, the primary care clinicians (general practitioners (GPs) and nurses) decide whether or not to prescribe an antibiotic: **prescription decision**. At this stage the GPs' and nurses' level of medical knowledge and adherence to guidelines for diagnosis and treatment are important as well as their inter-professional cooperation and agreement on a common management [89].

Third, when antibiotics are deemed necessary, the clinician decides what antibiotic to prescribe: **subtype decision**. GPs' expertise and adherence to guidelines play an important role in the choice of antibiotic. Knowledge of the local resistance level in the population is also required, which emphasises the importance of studies performed on primary care populations.

Fourth, the patient decides whether or not to collect the prescription, start the treatment and whether or not to complete the treatment: **intake decision**. At this stage the GP's ability to communicate instructions for treatment to the patient and inspire confidence is important. In the process of improving the quality of antibiotic use, insight into all of these steps is necessary in order to identify targets for intervention.

National guidelines

National guidelines for management of common infections have been developed by the Public Health Agency of Sweden and the Swedish strategic programme against antibiotic resistance (Strama) in collaboration with physicians in hospital and primary care. The guidelines outline evidence-based rules for diagnoses and treatment of common infections in primary care. They are revised regularly and promoted by the health authorities [90]. Strama carries out regular visits to most PHCCs in Sweden or organises meetings in order to implement and promote the national guidelines. Following national guidelines is regarded as good medical practice and helps improve quality in antibiotic prescribing.

Aims of the thesis

General aim:

To analyse different aspects of quality in the management of common infections in primary care with regards to antibiotic prescribing, antimicrobial resistance and adherence to guidelines.

Specific aims:

- Describe consultation rates and antibiotic prescribing for common infectious diagnoses in primary care in Sweden. Note trends over time and relate to adherence to national guidelines.
- Evaluate European disease-specific Antibiotic Prescribing Quality Indicators (APQI) for primary care using diagnosis linked prescription data from three European countries.
- Map current level of antimicrobial resistance of common respiratory tract pathogens in children in primary care and relate to antibiotic consumption.
- Analyse characteristics of national guidelines for three common respiratory tract infections in primary care and how general practitioners express how they relate to them.

Materials and Methods

Table 2.
Overview of studies.

Paper	I	II	III	IV
Design	Retrospective register study	Retrospective register study	Prospective cross-sectional study	Qualitative study
Study population	Patients registered at 88 PHCCs in Sweden. (n=785070) All ages.	Primary care populations in Belgium, the Netherlands and Sweden. All ages.	Children 0-10 y seeking primary care in southern Sweden, with symptoms of RTIs. (n=422)	GPs, age 34-67 years of age, from three geographical regions in Sweden. (n=29)
Data collection period	2008-2010-2013	2012	Nov 2013-April 2014 and Nov 2014-April 2015.	Jan-Feb 2014.
Data collection method	Analysis of data from the Primary Care Register of Infections (PRIS)	Analysis of data from primary care records in Belgium, the Netherlands and Sweden.	Prospective and descriptive study based on nasopharyngeal cultures and parental questionnaires.	Collection of guidelines and semi-structured interviews with GPs.
Data analysis	Proportions and standard deviations were used. Comparisons between proportions of categorical variables in more than two independent groups were performed with the Chi-square test for trend.	Calculations of descriptive data; consultation incidence and number of prescriptions per 1000 person years.	Comparisons between proportions of categorical variables in independent groups were performed with the Chi-square test. Multiple logistic regression analysis.	Template analysis according to Crabtree and Millar. Inductive analysis of the interviews.

Paper I:

This retrospective, descriptive study was based on the information retrieved from the Primary care Record of Infections in Sweden (PRIS) from the years 2008, 2010 and 2013.

The study population

The PRIS register was started in 2007 by the Unit of Research and Development in Jönköping with support from The Public Health Agency of Sweden and contains Sweden's largest database regarding diagnosis linked antibiotic prescription data. Primary Healthcare centres (PHCC) all over Sweden with a computerised journal system compatible with "the Rave system" were invited to participate in PRIS on a voluntary basis.

The number of PHCCs contributing data to the PRIS register was 47 in 2008, 58 in 2010 and 88 in 2013. In Sweden, there were about 1200 PHCCs in total in 2010. Together, the PHCCs represented in PRIS served 460,529 registered patients in 2008 and 785,070 in 2013, of all ages, in both urban and rural areas of Sweden. Accordingly, the number of registered patients in 2013 represented 8% of Sweden's total population of 9,644,864 inhabitants in 2013 [91] .

For each year all registered contacts were traced either due to the presence of an infectious diagnosis according to the International Classification of Disease and Related Health Problems- Tenth Revision (ICD-10), introduced by the WHO, or because an antibiotic prescription by Anatomical Therapeutic Chemical Classification (ATC)-code had been registered. The ATC coding system is used to classify drugs to facilitate studies of drug use in Sweden. With each registered encounter, information on the patient's age, sex and if applicable laboratory testing and antibiotic prescription were recorded. Only data during office hours of weekdays were recorded.

Data processing

In order to make a clear description on how antibiotics are prescribed in primary care the different diagnoses were divided into four groups according to infection type; respiratory tract including ear infections (RTI), urinary tract (UTI), skin and soft tissue (SST) and other infections.

RTIs were further divided into upper RTIs (URTIs) and lower RTIs (LRTIs). URTIs were organised into groups that share similarities in clinical practice or

national guidelines, such as common cold, sore throat, acute otitis media (AOM) and sinusitis. AOM was divided into age groups due to specific Swedish national guidelines regarding children 1-12 years old.

The LRTIs were divided into chronic obstructive disease (COPD), cough, acute bronchitis, pneumonia and influenza as these groups differ with regard to recommended treatment.

In order to calculate the number of antibiotic prescriptions per 1000 patient years (PY) each PHCC provided information on the number of registered patients at their clinic, calculated as a mean for each year. PY refers to the number of registered patients in the participating PHCCs, per year.

The variability in antibiotic prescription rate between different PHCCs for five common diagnoses (AOM, sinusitis, tonsillitis, acute bronchitis and pneumonia) was presented.

To control for a possible selection bias in the new PHCCs recruited to PRIS each year, a sensitivity analysis was provided by comparing data from the 37 PHCCs that had participated in PRIS for all three years to that of all PHCCs in PRIS. Percentage of consultations for infections, prescribed antibiotics and number of prescription per 1000 PY were calculated.

Statistical analysis

All analyses were performed using Excel (Microsoft. Microsoft Excel. Redmond. Washington: Microsoft, 2010. Computer Software) and SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp).

For descriptive statistics, proportions and standard deviations were used. Comparisons between proportions of categorical variables in more than two independent groups were performed with the Chi-square test for trend using an online calculator (www.epitools.ausvet.com.au). P-values ≤ 0.05 were considered statistically significant.

Paper II:

The study was based on primary care databases from Belgium, the Netherlands and Sweden containing diagnosis linked antibiotic prescription data.

Design

We conducted a retrospective observational study of primary care databases from three different countries. Calculation of the European disease-specific antibiotic prescribing quality indicators (APQI) values required databases with information on patients' gender, age, diagnosis and the antibiotic prescribed, with diagnoses labelled according to the revised second edition of International Classification of Primary Care (ICPC-2-R) [92,93] and antibiotic prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification [94].

The study period was one year (January 1 until December 31, 2012). For each diagnosis, we determined whether or not an antibiotic was prescribed, and which one. For quality and internal validity reasons, we noted the percentage of antibiotic prescriptions not linked to a diagnosis. These were 40% for Belgium, 16% for the Netherlands and 26% for Sweden.

Primary care databases

Belgian data were retrieved from the Intego Network that provides anonymous routine healthcare data (office hours of weekdays) from digital patient records of 51 general practices (94 GPs) located all over the region of Flanders, which all use the same medical record software (Medidoc).

Dutch data were retrieved from the Julius General Practitioners Network that provides anonymous routine healthcare data (office hours of weekdays) from digital patient records of 45 general practices (160 GPs) located in the centre of the Netherlands.

Swedish anonymised data were retrieved from all 52 general practices (212 GPs and interns/residents) located in Jönköping County (office hours of weekdays), which all use a common medical record (Cosmic) with a universal database.

Statistical analysis

Calculations of descriptive statistics were performed using Microsoft Excel 2010 and SPSS 21.

Consultation incidence and antibiotic prescriptions per 1000 patient years (PY)

The numbers of consultations/episodes coded with the diagnosis under study (ICPC-2-R code) (within age and gender limits) were divided by the numbers of patients (within the same limits) registered at the participating general practices and multiplied by 1000.

For Belgium, the number of registered patients for the general practices was not available. We instead used the number of patients contacting their general practice over one year (90, 839), according to the Intego database, and multiplied by 1.25. The factor of 1.25 has been calculated by comparing national reimbursement data with data from the Intego Network [95].

For each of the seven diagnoses, we calculated the number of antibiotic prescriptions per 1000 patient years (PY) by multiplying the number of consultations per 1000 PY (consultation incidence) by the percentage of prescriptions per diagnosis.

Disease-specific antibiotic prescribing quality indicators (APQI)

For seven acute infections (URTI, sinusitis, tonsillitis, otitis media, bronchitis/ bronchiolitis, pneumonia and cystitis) labelled with ICPC-2-R codes R74, R75, R76, H71, R78, R81 and U71, respectively (see Supplement 1 for the corresponding ICD-10 codes) ESAC proposed three quality indicators: (a) the percentage of patients (within specified age and/or gender groups) prescribed an antibiotic; (b) the percentage of patients (within specified age and/or gender groups) prescribed the antibiotic recommended by the European consensus, (c) the percentage of patients (within specified age and/or gender groups) prescribed quinolones [62]. For each of the 21 APQIs, a range of acceptable values was proposed. The acceptable ranges for (a) the percentage of patients prescribed an antibiotic were 0–20% for URTI, tonsillitis, sinusitis and otitis media, 0–30% for bronchitis and 80–100% for pneumonia and cystitis. The acceptable range for (b) the percentage of recommended antibiotic was 80–100%. For (c) the percentage of patients prescribed a quinolone the acceptable range was 0–5%. The recommended first-choice antibiotic for URTIs and tonsillitis were beta-lactamase sensitive

penicillins, for acute bronchitis, sinusitis, media otitis and pneumonia penicillins with extended spectrum, and for cystitis, nitrofurantoin or trimethoprim. We compared the country's APQI values with these proposed ranges of acceptable values [62].

Exclusion of one indicator

In a previous study, it was found that the interpretation of indicator 7a (the percentage of patients receiving an antibiotic for pneumonia) could be hampered due to additional diagnostic investigations and/or hospital referral before starting antibiotic treatment [96]. Therefore, we present the figures for indicator 7a but excluded them from the overall quality assessment.

Paper III:

We performed a cross-sectional study to investigate the level of resistance in respiratory tract pathogens of children in primary care by collecting nasopharyngeal samples and relating to antibiotic consumption via information obtained from parental questionnaires.

The study population

Nasopharyngeal cultures were obtained from children, 0-10 years of age, seeking care at their PHCC with symptoms of RTI between 1st Nov 2013 and 30th April 2015. The study included children registered at 12 different PHCCs in the county of Scania, which is in the southernmost part of Sweden.

The sizes of the PHCCs varied from two up to 15 serving physicians. The PHCCs were chosen to represent both urban and rural areas of the region, including the city of Malmö with approximately 320,000 inhabitants. The antibiotic prescription rates of the PHCCs were similar to the average prescription rate of the county. In 2013 the county of Scania had a population of 1,274,069 inhabitants, of which 167,484 were children aged 0-10 years [97].

Questionnaires

The parents were asked to fill out a questionnaire regarding factors believed to affect the bacterial resistance, such as the child's age, antibiotic consumption over the last year and specifically during the last four weeks, type of day care, number of siblings, travel abroad, hospital admissions etc. The same patient was only included once. The individual antibiotic consumption was evaluated via the questionnaire filled out by the parents. Lack of knowledge of the Swedish language was the only exclusion criterion.

Sample collection and bacterial analysis

Trained laboratory personnel at the PHCCs obtained NP specimens in a standardised manner. A swab (ESwab™ Liquid Amies Collection and Transport System, COPAN) [98] was taken from the rear wall of the nasopharynx, where the stick was kept still for 10 seconds before being withdrawn. The test swab was kept in a refrigerator until being sent to the Department of Clinical Microbiology in Malmö/Lund where it was analysed for *S.pneumoniae*, *H.influenzae*, *Moraxella catarrhalis* and Group A beta-haemolytic streptococci (GAS), according to national recommendations [99]. Antibiotic susceptibility testing was performed according to recommendations of the EUCAST [100]. Isolated *S.pneumoniae* were screened for penicillin resistance by disc diffusion test using 1-microgram oxacillin discs. Minimum inhibitory concentration (MIC) for benzyl penicillin was determined by the E-test in isolates with inhibition zones <20 mm. *S.pneumoniae* with MIC of ≥0.125 mg/L was considered penicillin non-susceptible (PNSP). Screening for beta-lactam resistance in *H.influenzae* was performed by disk diffusion test using benzyl penicillin discs. If found to be benzylpenicillin resistant, a beta-lactamase test was perfomed (Nitrocefin). For detection of chromosomal penicillin resistance (BLNAR), a disk diffusion test was used with a beta-lactamase stable cephalosporin (cefaclor) as an indicator.

In this paper, colonization with resistant bacteria was defined as the presence of PNSP and/or *H.influenzae* strains with beta-lactamase production and/or *H.influenzae* with chromosomal resistance (BLNAR).

Statistical analysis

The main outcome was the presence of PNSP and resistant *H.influenzae* in the NP culture. Questionnaire and laboratory data were collected in Microsoft Excel and statistical analysis was performed using SPSS 22.0 software (IBM, Armonk, NY, USA). Descriptive statistics are presented as numbers and proportions.

Comparisons between proportions for categorical variables in two independent groups were performed using the two-sided χ^2-test. Multiple logistic regressions were used to model the relationship between the outcome variable (carriage of resistant bacteria) and several independent variables.

Paper IV:

We chose a qualitative approach to explore the guidelines and GPs' stated adherence to the three different guidelines for lower respiratory tract infections (LRTI), acute otitis media (AOM), and acute tonsillitis. This included analysis of the current guidelines as well as analysis of semi-structured interviews with GPs. The interviews with GPs were conducted as part of a larger study of mixed method design, exploring factors influencing antibiotic prescribing [89].

Data collection and analysis

The characteristics of the guidelines for LRTIs, AOM, and tonsillitis were analysed with a template analysis [101] originating from six of the seven intrinsic attributes associated with compliance identified by Grol et al [74] These attributes are; concrete description of the desired performance, vague and not specific guidelines, complexity (complex decision tree with many different elements), new competence or skill needed, consequences for practice management (extra resources) and changing routines and habits needed. The attribute 'compatibility to existing norms and values' could not be evaluated by analysing the guidelines but were instead evaluated through the interviews. Three of the researchers determined independently whether the attributes were present or not in the studied guidelines. Disagreement was solved in discussion until consensus was achieved.

During January and February 2014 a strategic sample of 29 GPs from eight PHCCs in three different counties in Sweden were interviewed. The GPs represented a variety of gender, age, educational background, working experience, urban/rural location of the PHCCs as well as areas with high and low antibiotic prescribing. All participating PHCCs were publicly run. All GPs invited to be interviewed agreed to participate.

Individual semi-structured interviews with open-ended questions to ensure to stimulate the interviewees' own narratives were performed. The topics for the interviews were management of patients with cough, earache, and sore throat in primary care with reference to national guidelines. Four researchers were GPs and

two were social scientists. The interviews were audio recorded and transcribed verbatim by a professional secretary.

The interviews were analysed inductively in relation to guidelines to find themes relevant for adherence/non-adherence to guidelines [102]. The resulting themes from the analysis of the guidelines were then compared with the attributes defined by Grol et al, which they corresponded to.

The analysis was an iterative process with discussions among the researchers during several meetings until consensus was reached. The analysis was performed manually.

Ethical considerations

All persons participating in the projects were as far as possible, asked for consent to participate. Regarding the children, (**Paper III**) their parents were asked to sign a consent form. All participation was voluntary with the possibility to withdraw at any time. In the register studies (**Paper I and II**) it was not possible to ask everyone for their consent to participate, but all data were anonymised and one-way encrypted so that no data could be traced back to any participant and confidentiality could be maintained. All data from the studies are kept in locked devices, according to regulations. The studies conform to the principles outlined in the Declaration of Helsinki.

Paper I

Confidentiality for patients was ensured by one-way encrypted ID-number. Ethical approval for the PRIS register was obtained from the Regional Ethical Review Board in Linköping, Sweden. (Dnr 2010/ 227-31)

Paper II

Belgian data:

The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven under N° ML1723 and approved compliant with the law according to the Sectorial Committee "Health" of the Belgian privacy commission (decision no. 13.026, March 19, 2013).

The Netherlands data:

Julius Centre for Health Sciences and Primary Care started collaborations with the medical practices participating with data many years ago. At that time an ethical approval was obtained in order for Julius Centre to be able to extract data from the register for routine quality control. Information about the data register was available at each medical practice and the patients were free to opt out at any time.

Swedish data:

Confidentiality for patients was ensured by one-way encrypted ID-numbers. No analyses were performed for individual patients. The identity of the health centres was also encrypted and only used in anonymous comparisons between them. The

study data was part of a national database for quality surveillance and no ethical committee approval was considered necessary.

Paper III

Information about the study and a written invitation was given to the parents at arrival to the clinic and written informed parental consent was retrieved for each case. The study was approved by the Regional Ethical Review Board in Lund, Sweden (Dnr. 2013/ 513).

Paper IV

Participation was voluntary. All participants gave their written informed consent to participate by replying to a written invitation. All data were treated confidentially and could not be traced to any named person. The study was approved by the Regional Ethical Review Board in Lund, Sweden (2013/679).

Results

Main findings

- The antibiotic prescribing rate for respiratory tract infections decreased while those for urinary tract infections and skin- and soft tissue infections were unchanged. All the diagnoses regarding upper respiratory tract infections showed a decrease in both consultation and prescription rate during the years 2008-2013. Figures suggested increased adherence to national guidelines for acute otitis media, lower respiratory tract infections and tonsillitis. **(Paper I)**
- We found that it was feasible to calculate the European disease-specific Antibiotic Prescribing Quality Indicators (APQIs) from routine data originating from Electronic Patient Records. The APQIs can be used to identify improvement areas but need to take into account consultation incidence and national guidelines for each country. **(Paper II)**
- The prevalences of PNSP and resistant *H.influenzae* among respiratory tract pathogens in children with symptoms of RTIs in primary care were low, indicating that penicillin V is valid as empirical treatment for these patients, if antibiotics are required. Antibiotic treatment within the previous four weeks predisposed for resistant bacteria. **(Paper III)**
- The guidelines showed different characteristics. The crucial attribute for adherence seemed to be compatibility to existing norms. GPs' persisting concepts need to be addressed when creating national guidelines as they could otherwise act as a barrier to adherence. **(Paper IV)**

Trends in antibiotic prescribing in Sweden (Paper I)

Although the consultation rate for all infections remained around 30% each year, antibiotic prescribing rates decreased significantly over the years from 53.7% in 2008 to 45.5% in 2010 to 38.6% in 2013 (p=0.03). Particularly, for respiratory tract infections (RTIs) the prescribing rate decreased from 40.5% in 2008 to 24.9%

in 2013. The number of antibiotic prescriptions per 1000 PY decreased significantly for RTIs but remained unchanged for urinary tract infections (UTIs) and skin- and soft tissue (SST) infections.

For all RTI diagnoses except pneumonia there was a decrease in prescription rate from 2008 to 2013. The number of consultations as well as the number of antibiotic prescriptions per 1000 PY for the diagnoses common cold, sore throat, AOM and sinusitis decreased simultaneously over the years. (Figure 5)

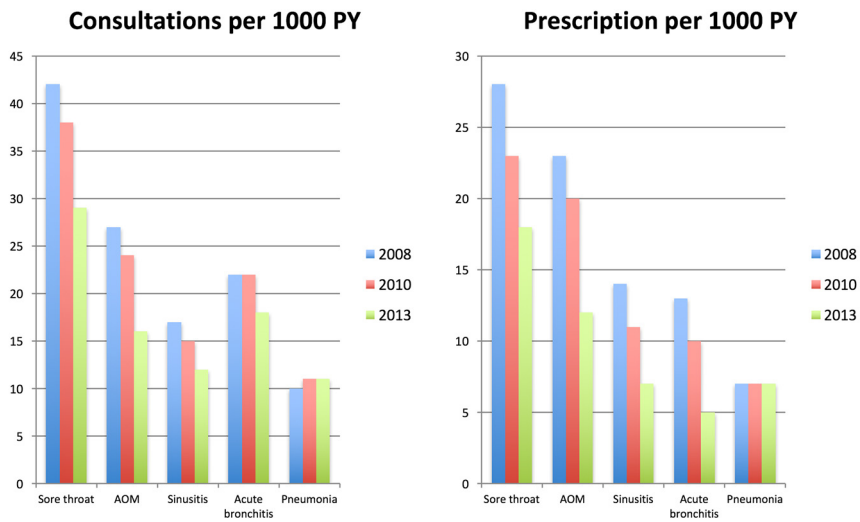

Figure 5.
Consultations and antibiotic prescriptions per 1000 patient years (PY) for common respiratory tract conditions in Swedish primary care for the years 2008, 2010 and 2013.

Penicillin V was the antibiotic most often prescribed for RTIs, followed by tetracycline. The proportion of Penicillin V increased and all other antibiotic subclasses decreased from 2008 to 2013. (Figure 6)

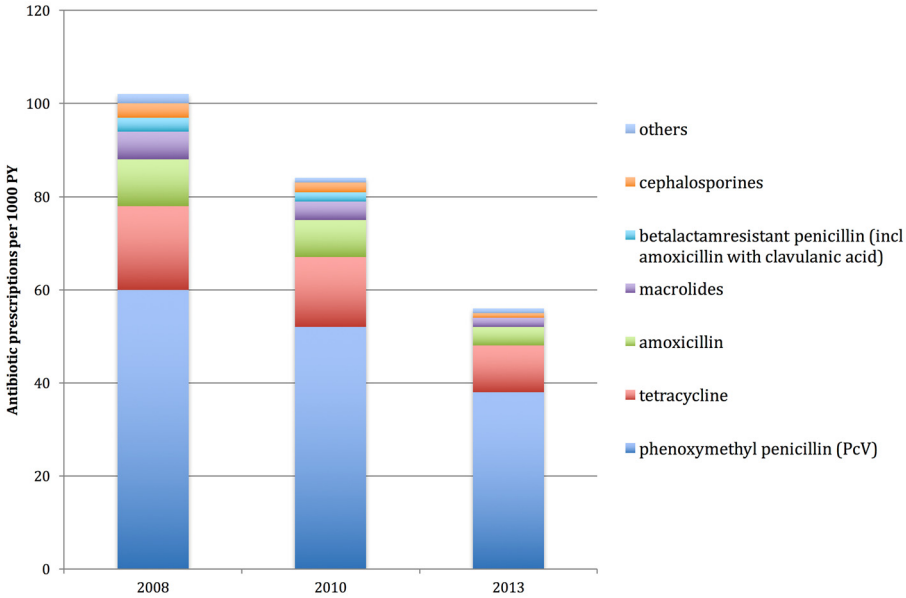

Figure 6.
Trends of antibiotic prescriptions divided into subclasses for treatment of RTIs in the years 2008, 2010 and 2013.

Tonsillitis and acute otitis media (AOM) were the two RTI diagnoses with the highest number of prescriptions per 1000 patient years (PY). For these diagnoses, an increase in adherence to national guidelines was seen with regards to treatment frequency, choice of antibiotics and use of rapid antigen detection test.

The number of antibiotic prescriptions per 1000 PY for AOM was halved between 2008 and 2013. Children 1-12 years of age comprised about two-thirds of the cases of AOM for all three years. The fraction given no antibiotics increased significantly from 15.4% in 2008 to 27.0% in 2013 (p=0.04) and the percentage of patients treated with Penicillin V increased from 73.6% in 2008 to 84.5% in 2013. (Figure 7)

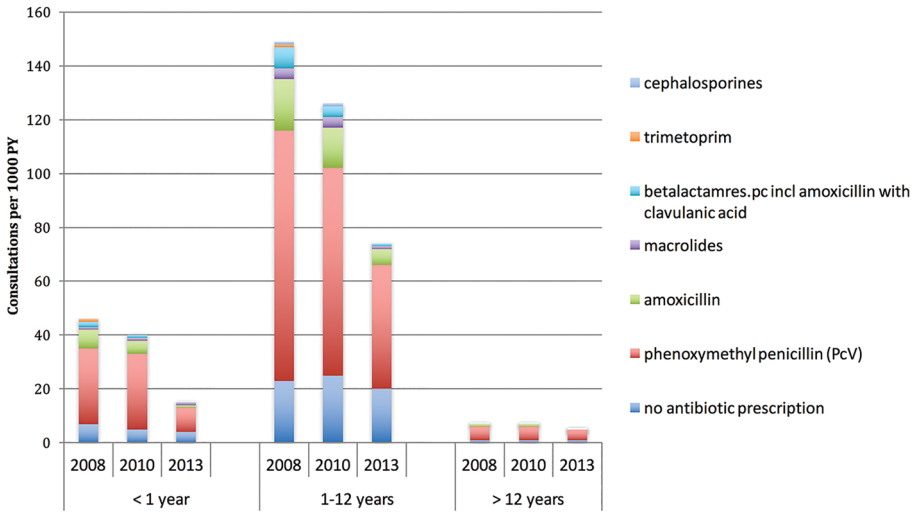

Figure 7.
Trends in consultations and antibiotic prescribing for treatment of AOM according to age group in the years 2008, 2010 and 2013.

The antibiotic prescribing rate per diagnostic group varied between different PHCC. The largest difference between the lowest and the highest prescribing PHCC was found for the diagnoses bronchitis and sinusitis.

Antibiotic prescribing in Belgium, the Netherlands and Sweden (Paper II)

From the databases used in the second paper, we noted some differences in consultation incidence (number of consultations per 1000 registered patients) as well as antibiotic prescribing between Belgium, the Netherlands and Sweden. For the seven diagnoses under study (URTIs, sinusitis, tonsillitis, AOM, bronchitis, pneumonia and UTIs) the total consultation incidences were highest in Belgium and lowest in Sweden. (Table 3)

Table 3.
Country specific data and characteristic of dataset.

Country	Belgium	Netherlands	Sweden
Population in whole country (2012) (source: www.statista.com)	11.1 million	16.7 million	9.6 million
DID* (year 2012)	29.8	11.3	14.1
PID** (year 2009)	2.53	1.53	1.19
No of practices in study	46	45	52
No of GPs in study	94	160	212
Total no of patients registered with the practices	113549***	266 417	338 149
No of consultations (diagnosis in study with gender and age limitations)	34 044	55 529	59 534
Total no of consultations per 1000 PY****, (diagnoses in study with gender and age limitations)	341	329	243
Total no of prescriptions per 1000 PY**** (diagnoses in study with gender and age limitations)	189	170	138

* Defined Daily Dose (DDD) per 1000 inhabitants per day, reference 6, Paper II.
**Number of packages per 1000 inhabitants per day, reference 6, Paper II.
***Estimated according to reference 15 in Paper II.
****Patient Years (PY) refers to the number of registered patients in the participating practices.

By combining consultation incidences and prescribing percentages, the numbers of prescriptions for the individual diagnoses can be calculated per 1000 PY. Belgium had the highest number of prescriptions per 1000 PY for URTIs and bronchitis, the Netherlands for sinusitis and cystitis, and Sweden for tonsillitis and pneumonia. For otitis media, this number was roughly similar for all three countries.

We noted that high consultation incidences for a particular diagnosis were associated with high numbers of antibiotic prescriptions per 1000 PY per diagnosis. (Figure 8 and 9) Unfortunately, the datasets were not complete as 40% (Belgium), 26% (Sweden) and 16% (the Netherlands) of the prescriptions lacked diagnoses for each respective country.

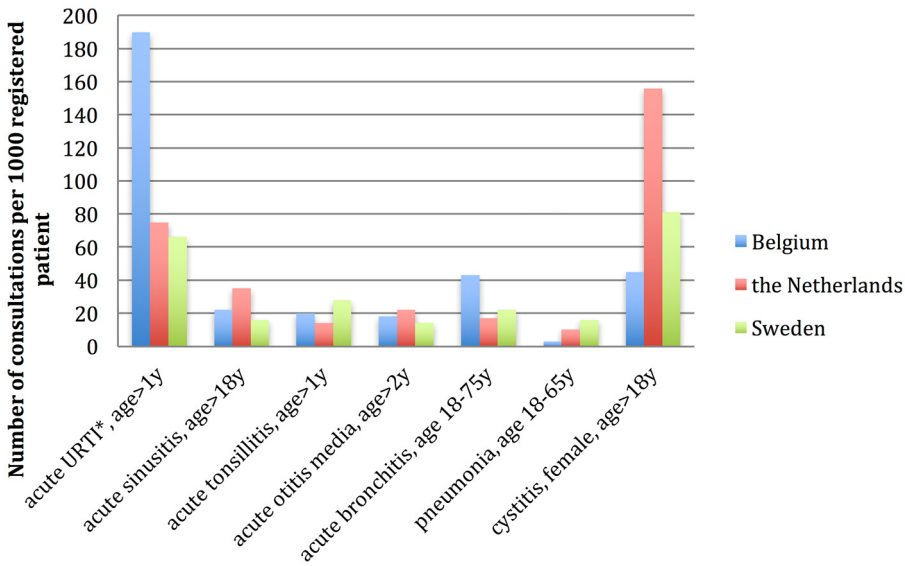

Figure 8.
Number of consultations per 1000 registered patient for the seven diagnoses under study in Paper II.

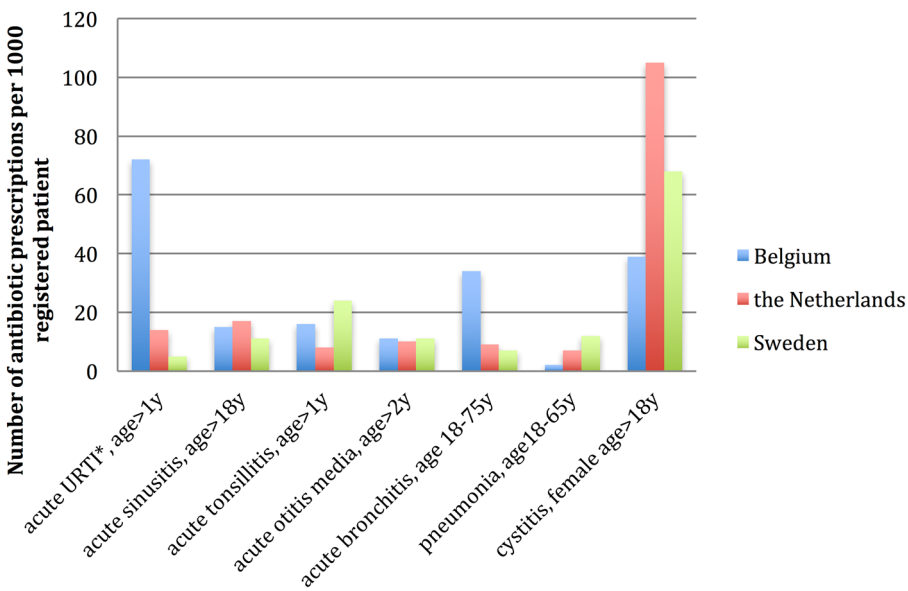

Figure 9.
Number of antibiotic prescriptions per 1000 registered patient for the seven diagnoses under study in Paper II.

Evaluating European Antibiotic Prescribing Quality Indicators (Paper II)

For the 20 APQIs in the analysis, 16 (Belgium), 10 (the Netherlands) and 9 (Sweden) values exceeded the respective ranges of acceptable values.

Indicator a (percentage prescribed antibiotic per diagnosis)

For sinusitis, tonsillitis and AOM the percentage of prescribed antibiotic was higher in Sweden (>70%) compared to Belgium (>60%) and the Netherlands (>45%). But due to the low consultation incidences, the number of prescriptions per 1000 PY was still low in Sweden. Sweden had the smallest proportion of antibiotic prescriptions for bronchitis (33%) and URTIs (8%).

Indicator b (percentage prescribed the antibiotic recommended by the European consensus)

Regarding choosing the recommended antibiotic according to the European consensus of the APQI, very few were in the acceptable range; none of the diagnoses in Belgium, three of the seven diagnoses in the Netherlands and only two of the Swedish diagnoses. Using the antibiotics recommended in the national guidelines improved the results of the indicator regarding percentage of first choice antibiotic significantly, from 22% to 82% for sinusitis in the Netherlands and from 41% to 94% for cystitis in Sweden.

Indicator c (percentage prescribed quinolones per diagnosis)

Quinolones are strong drivers of resistance and therefore not recommended as a first line drug. In Belgium, quinolone prescribing was higher than the acceptable level of 5% for sinusitis, bronchitis, pneumonia and cystitis. Only for cystitis was the 5% upper limit of acceptable quinolone prescribing exceeded in the Netherlands. None of the indications exceeded the 5% upper limit of acceptable quinolone prescribing in Sweden.

Bacterial resistance in a primary care population (Paper III)

Prevalence of pathogens and resistance

Altogether, 422 children were recruited of which 340 participated with a NP culture and the parental questionnaire. A total of 82 children did not accept having nasopharyngeal culture taken (Figure 10). The baseline characteristics of the children with and without a nasopharyngeal culture taken were similar. The median age in both groups was 2.0 years (IQR=1-5).

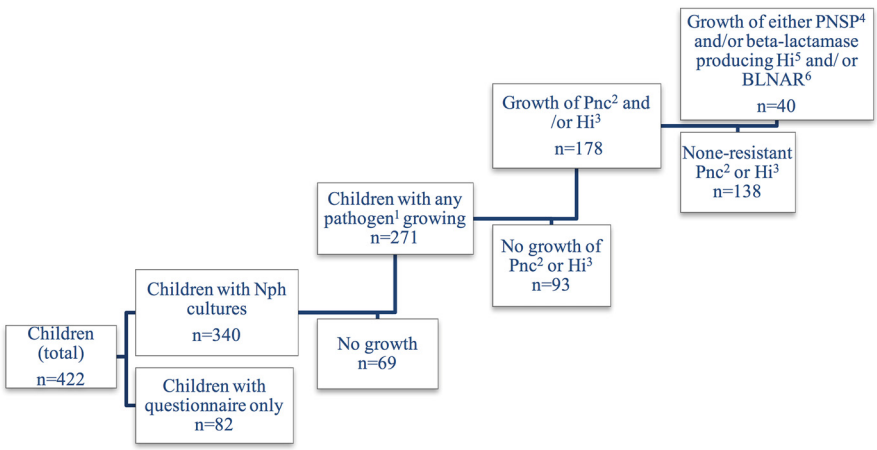

Figure 10.
Flow chart of children in the study. [1]Either *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* or Group A beta-hemolytic Streptococci. [2] *Streptococcus pneumoniae.* [3], *Haemophilus influenzae.* [4]penicillin non-susceptible *Streptococcus pneumoniae.* [5] *Haemophilus influenzae.* [6] beta-lactamase negative amoxicillin resistant *Haemophilus influenzae.*

Of the 340 children, 86 (25%) carried *S.pneumoniae*, 129 (38%) *H.influenzae*, 185 (54%) *M.catarrhalis*, 24 (7%) beta haemolytic streptococci group A and 69 (20%) apathogenic or no bacteria. Of the 86 isolates with *S.pneumoniae*, five (6%) were PNSP all with MIC=0.125 mg/L. Three of these PNSP isolates also showed resistance to trimethoprim, one showed additional resistance to tetracycline and one additional resistance to tetracycline, erythromycin and clindamycin.

Comparison with data from the local clinical microbiology laboratory

The prevalence of *S.pneumoniae* and *H.influenzae* were similar to the data from the local clinical microbiology laboratory for the same period and age group (Table 4). We could not identify any statistically significant difference in prevalence of PNSP (p=0.31), beta-lactamase producing *H.influenzae* (p=0.33) or BLNAR (p=0.08) between our community study and the data from the local clinical microbiology laboratory. (Table 4)

Table 4.
Data on isolated bacteria in nasopharyngeal cultures of children 0-10 years during November 2013-April 2014 and November 2014-April 2015, in the study and in routine laboratory data.

	Our data (primary care)	Routine laboratory data (primary care and hospital care)
Number of cultures	340	1854
Streptococcus pneumoniae	86 (25%)	468 (25%)
PNSP* (MIC≥0.125 mg/L)	5 (6%) All with MIC=0.125mg/L	47 (10%) Of which: 32 MIC=0.125mg/L 6 MIC=0.25mg/L 4 MIC=0.5mg/L 4 MIC=1mg/l 1 MIC=2mg/L
Erythromycin resistant	4 (5%)	32 (7%)
Clindamycin resistant	3 (3%)	25 (5%)
Tetracycline resistant	4 (5%)	23 (5%)
Trimethoprim resistant	7 (8%)	53 (11%)
Haemophilus influenzae	129 (38%)	747 (40%)
Beta-lactamase producing	21 (16%)	96 (13%)
BLNAR**	16 (12%)	57 (8%)
Moraxella catarrhalis	185 (54%)	1524 (82%)
Group A beta-haemolytic streptococci	24 (7%)	138 (7%)

*penicillin non-susceptible pneumococci
**Beta-lactamase negative ampicillin resistant *Haemophilus influenzae*

Factors associated with resistant bacteria

When analysing all 340 children, who provided NP cultures, we found that having received antibiotic treatment (predominately Penicillin V) within the previous four weeks predisposed for resistant bacteria, OR=3.08, 95% CI (1.13-8.42). Antibiotic consumption during the last year did not significantly affect the prevalence of resistant bacteria in our analysis. But, since it could interact with the variable antibiotic consumption the previous four weeks we decided to exclude it in the regression analysis. The risk of carrying resistant bacteria also decreased with age, OR=0.75, 95% CI (0.57-0.99).

In 178 of the cultures, there was growth of either *S.pneumoniae* or *H.influenzae* or both, of which 40 isolates showed some sort of resistance to beta-lactam antibiotics, either PNSP, and/or beta-lactamase producing *H.influenzae* and/or BLNAR. (Figure 10)

When analysing only the 178 children with growth of either *S.pneumoniae* or *H.influenzae*, or both, we noted that boys were more commonly colonised with resistant bacteria, OR=2.95, 95% CI (1.25-6.98). No significant association was found between resistance and hospital care, travelling abroad, parental smoking, day care attendance, respiratory tract disease (asthma/allergy) or pneumococcal vaccination.

Guideline characteristics and GPs' stated adherence (Paper IV)

The analysis of the guidelines showed differences concerning the presence of the attributes (Table 5). The guideline for acute tonsillitis was the most concrete and had the most detailed descriptions of the desired performance while the guideline for LRTI was more vague. The guideline for AOM was the most complicated and the only guideline requiring partly new equipment and new skills.

Table 5.
Characterization according to evidence in the literature of the Swedish guidelines for diagnosis of lower respiratory tract infections (LRTI), acute otitis media (AOM) and tonsillitis (Grol et al. 98)

	Presence of characteristics		
	LRTI	AOM	Tonsillitis
Concrete and precise description of the desired performance	No	Yes	Yes
Vague and not specific	Yes	No	No
Complex (composed of many different elements, contains a complex decision tree or conditional factors)	No	Yes	No
Demands acquision of new competence or skill	No	Yes	No
Consequences for practice management (new equipment)	No	Yes	No
Demands changing routines and habits	No	Yes	No

The characteristics of the 29 interviewed GPs are presented in Table 6.

Table 6.
Description of the 29 interview participants.

Category	Variable	Number of participants
Age	<45	7
Gender	Female	13
Medical education	In Sweden	19
Location of practice	City	8
	Town	16
	Village	5
Antibiotic prescription level in the county	High level	13
	Medium level	3
	Low level	13

In the inductive analysis of the interviews, four themes were found relevant for adherence to guidelines: knowledge of guidelines, clinical skills, organisational flow and persisting concepts. The theme 'guideline knowledge' was found to correspond to the attributes concrete or vague description and complexity of decision-making. The theme 'organisational flow' corresponded to consequences for practice management and demands to change routines and habits and the theme 'persisting concepts' to conformity to existing norms and values.

Concrete or vague description and complexity of decision-making

Analysis of the guidelines

The analyses of the guidelines showed that the guideline for tonsillitis had the most concrete and detailed descriptions presented in a flowchart (Table 5). This

was also the guideline that implied the least complex decision-making. The guideline for LRTI was assessed as the opposite: It was the most vague guideline with few detailed descriptions. The guideline for AOM was quite detailed and concrete but contained, at the same time, a complicated message with many different elements. Taking these attributes into account the guideline for tonsillitis would be best complied with.

Analysis of the interviews

From the interviews, we noticed that all GPs expressed knowledge about all three guidelines but in their reported management of the three patient cases we found that the adherence differed to varying degrees.

The guidelines for LRTI seemed to be known and well adhered to in general. When discussing LRTIs the focus for the GPs was on identifying pneumonia among a wide range of differential diagnoses, which is in line with the guideline. Despite the vaguely described and rather complex diagnostic procedure, the GPs did not report any problem in diagnosing pneumonia. However, the guideline's concrete recommendation to use O2-saturation and breathing frequency was not commonly addressed by the GPs in the interviews.

Regarding management of patients with earache, the GPs focused on visually assessing the eardrum in line with the guideline. However, they did seldom mention the importance of mobility, which the guideline emphasised. Several GPs referred to the guidelines being applicable for certain ages but had difficulties in remembering which ones. Others did not seem to be aware that age was part of the criteria for treatment. The guideline was described as complicated and therefore difficult to internalise and follow.

The guideline for tonsillitis aim to detect Group A beta-haemolytic streptococci (GAS) induced tonsillitis and it requires at least three Centor criteria to take a RADT for GAS and if RADT indicates positive for GAS antibiotics are recommended. Despite these concrete descriptions of the desired performance, many GPs only reported one or two Centor criteria. Thus, the criteria did not guide in the use of RADT, which contrary to the guideline was used when suspicion of tonsillitis was low and only few criteria present. Moreover, clinical findings could overrule the guidelines' recommendation to use RADT.

> B: And…if I have met a patient who fits the criteria and if I have found something objective and precise…I…the most important thing for me is the clinical status.
>
> B: How the patient is feeling, is affected…and so if I find something by objective examination, when I look at the throat, that…for example, I take no samples, I treat directly.

A negative RADT for GAS was seldom mentioned as a facilitator to avoid an antibiotic prescription.

Acquisition of new competence, consequences for practice management and demands to change routines and habits

Analysis of the guidelines

Only the guideline for AOM contained recommendations requiring partly new skills in conjunction with new equipment, which in turn potentially called for organisational change. The guideline recommends eardrum mobility to be assessed through pneumatic otoscopy, ear microscopy or tympanometry. The guideline for LRTI and tonsillitis contained no additional need for new skills or organisational change.

Analysis of the interviews

From the interviews, we found that the recommended diagnostic tools for diagnosing AOM were rarely used. In quite a few health centres equipment for pneumatic otoscopy was lacking in the GPs' office. In addition to learning the skill to use the equipment, the ear microscope or tympanometry were located in a special room in the health centre. The GPs, however, preferred to stay in their room for the whole consultation both due to habit and lack of time. Thus both lacking the new skill and loathing the organisational change hampered adherence.

Compatibility with existing norms and values

Analysis of the interviews

The interviews addressed compatibility to existing norms and values. For patients with LRTI and tonsillitis, many GPs mentioned the important challenge to differentiate the conditions into viral or bacterial in order to conclude who needed antibiotics, which we interpret as expressing a norm where bacteria always needs to be identified and treated. Near patient CRP was regarded an important tool used to differ between bacteria and virus. This is in line with the guidelines for LRTI but the GPs use of CRP in relation to tonsillitis is contrary to the guidelines where CRP is not recommended.

In accordance with the recommendations of the guideline for LRTI, CRP was used early on in the clinical assessment of these patients. The diagnosis of acute bronchitis was associated with a viral origin and pneumonia with bacterial corresponding to the result of the CRP tests.

> B: Yes, if I have a patient with a cough and if I suspect infection…I take CRP…I first want to see what exactly it looks like…it can be that you have a cough…but the inflammation…it's viral inflammation.
>
> B: So it's not completely certain that it's bacteria.
>
> B: So CRP…sometimes it helps us because you…well, it can be…bacterial that's needed…

In patients with otitis media, however, almost none mentioned the need to differentiate into viral or bacterial condition. The crucial point stated was to identify a condition with red eardrum diagnosed as acute otitis media. Most GPs seemed to have accepted the self-healing character also of bacterial origin of AOM and were not too worried about complications. GPs stated no conflict with their existing values.

For many GPs the guidelines for acute tonsillitis did not seem to be compatible with existing values. For example, many GPs did not appear to believe that tonsillitis is a self-healing condition and they had great trust in antibiotic treatment being beneficial to avoid complications, which can be put in contrast to the guidelines statement that treatment of tonsillitis is performed in order to shorten symptoms duration. Some GPs described how they differed between virus and bacteria using their clinical gaze instead of using the recommended Centor criteria.

> B: If it (strep A) is negative and the clinical picture indicates bacterial infection…and the patient has a temperature, if the patient feels tired, if the patient has difficulty swallowing…I give antibiotics.

Others told of using the non-recommended CRP. CRP seemed to be regarded as a superior test that could confirm or exclude significant bacterial disease. GPs also told of patients asking for RADT testing regardless of Centor criteria.

> B: And…sometimes patients come just to…they want to take a throat sample.
>
> B: So then the sample is more some form of…well…a way to make the patient secure and satisfied, that's how it is.
>
> A: Mmm.
>
> B: But…I understand that too, that in…in the long run it would have been better to devote a little time and perhaps explain why you shouldn't take this sample, but the thing is how little…time you have and what contact you think you get with the patient.

Compatibility with existing norms thus varied between the guidelines and a conflict between guidelines and existing norms seemed most pronounced for tonsillitis.

Interference with GPs' decision making, compatibility with existing norms and adherence to guidelines

Analysis of the guidelines and the interviews

We noted that a concrete description might interfere with the GPs' decision making to a different extent. There is more room for the GPs' idiosyncratic interpretation when the diagnostic process is not transparent but includes segments exclusively performed and interpreted by the doctor, for example examining the eardrum or auscultation of the lungs. Less room for interpretation is given when tests or other measures are used to validate the diagnostic process and this characterises the guideline for tonsillitis to a high degree.

We found that if the recommendation in the guidelines was not compatible with existing norms, the adherence was low regardless of all the other attributes. This was most pronounced for tonsillitis (Figure 11). The low adherence for the tonsillitis guideline, expressed in the interviews, seemed to be further disclosed by the constraint laid on the GPs' decision making by the recommendation to use the Centor criteria and the near patient test RADT. For AOM the GP made the diagnosis alone with large possibilities for free interpretation. Non-adherence was reported as diagnostic mobility test was omitted and recommended concrete indications for antibiotic treatment not remembered by the GPs. For LRTI few exceptions to the guideline were reported and use of near patient testing (CRP) was in line with existing norms.

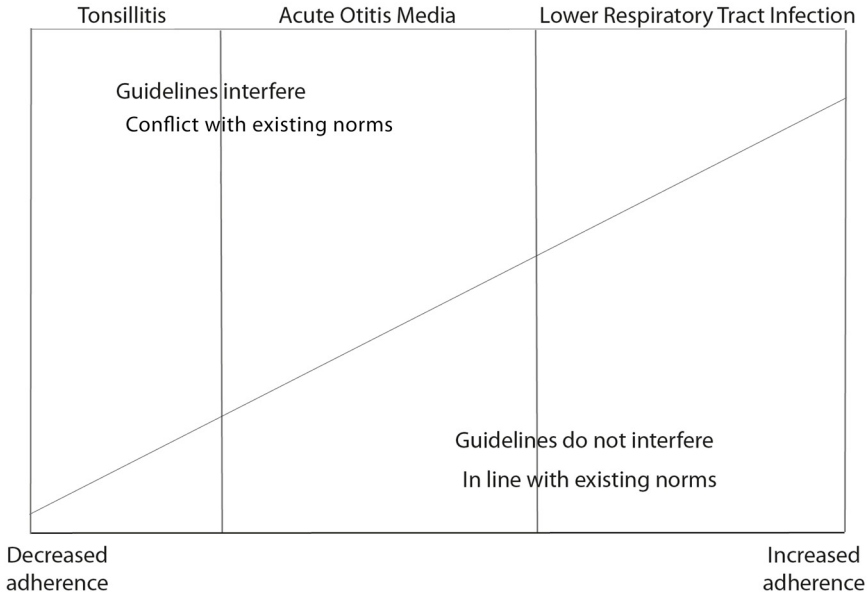

Figure 11.
Guideline interefence with excisting norms in three different guidelines (tonsillitis, AOM and RTIs).

Discussion

Main findings

We noted improved adherence to national guidelines for the most common RTIs in primary care. Reduced numbers of consultations and antibiotic prescriptions for RTIs between 2008-2013 was seen. (Paper I)

Comparing quality in antibiotic prescribing between countries using European common indicators proved to be challenging and required consideration of consultation incidence and national guidelines for each country. (Paper II)

The prevalence of PNSP (MIC≥0.125 mg/L) and resistant *H.influenzae* in children in primary care was low. We noted no significant differences in prevalence in PNSP and resistant *H.influenzae* in our results compared to the local microbiological laboratory. An increased OR for bacterial resistance was seen in children treated with antibiotics four weeks previously. (Paper III)

Interviews with GPs showed that persisting conceptions about how to diagnose and treat common infections in primary care still remain and need to be addressed further. Guidelines that interfere with the physician's diagnostic process seemed to override previously known beneficial characteristics of guidelines and were more difficult to gain acceptance for. (Paper IV)

Methodological considerations

In **Paper I** we evaluated current status of antibiotic prescribing in Swedish primary care and identified trends over the years 2008 to 2013. The strength of the study was that we used the largest register of diagnosis-linked prescription data available in Sweden. The data were based on over a million consultations to primary care of which 30% concerned infections. The database included almost 800 000 registered patients in 2013 which represents about 8% of Sweden's population and we therefore consider the results to be inferable to the country's population in general.

The limitations were that the participation in the register was voluntary and there was a risk that the participating PHCCs were more interested in monitoring their antibiotic prescriptions and also better prescribers. But, since the register included private and public PHCCs with both high and low prescription levels, as well as both rural and urban situated from different geographic regions of Sweden, the risk should be minimized.

A limitation with register studies (**Paper I** and **Paper II**) is the diagnostic process. Different physicians evaluate patients' symptoms and signs differently, and decide on different diagnoses for similar cases. Furthermore, sometimes a diagnosis is chosen to justify an antibiotic prescription. Cultural differences as to what symptoms are regarded as important to seek health care for seem to differ between countries (**Paper II**) and certainly effects the consultation incidences.

The datasets used in **Paper II** were not complete, as 40% (Belgium), 26% (Sweden) and 16% (the Netherlands) of the prescriptions lacked diagnoses for each respective country. Incompleteness of data, in the form of missing diagnoses, is a common problem when studying register data. The structure of the medical organisation, doctors' accuracy and ability and other factors are likely to affect diagnoses registration. In the PRIS database in **Paper I** about 14% of the antibiotic prescriptions did not have a diagnosis linked to it. For the Swedish data in both **Paper I** and **Paper II** we analyzed the antibiotic prescriptions, which lacked diagnoses and found that they comprised mostly of antibiotics prescribed without a physical consultation registered. We speculate that those prescriptions were made after test results such as cultures or x-rays became available or to nursing homes, over the phone.

The strength of **Paper III** was that data were based on a strict primary care population. The limitation was the difficulty to recruit patients due to lack of time among the personnel at the PHCCs. Most parents agreed to answer the questionnaire. Those who chose not to participate with a nasopharyngeal swab acted as control subjects, and they turned out to show similar characteristics as the children participating with a swab.

The strength of **Paper IV** was that the three guidelines we compared all had similar baseline conditions regarding how they were developed and distributed which made their intrinsic characteristics comparable. Furthermore, the strategic sample of GPs regarding gender, age and educational background should make the result transferable to the population of Swedish GPs. The study builds only on the statements from the GPs and we had no data on their performance. However, our findings are in line with earlier studies on performance in Swedish primary care [77,89].

If the interviews would have been less structured we might have received more information on the GPs thoughts about clinical guidelines. But, we would then probably have had to limit the number of interviews analysed. If we were to have used focus groups we would have lost the strategic sample of GPs and the transferability of the results mentioned above.

Adherence to guidelines

In **Paper I** we noted an increased adherence to national guidelines regarding acute bronchitis, AOM and tonsillitis. Adherence to national guidelines is regarded as good quality in antibiotic prescribing on a group level. Each patient consultation always requires an individual evaluation.

The national guidelines for diagnosis and treatment of common infections in primary care are produced via a process of workshops and meetings between the Public Health Agency, the organisation of Strama and other experts from both hospital and primary care. The literature is reviewed and the best available evidence is gathered to support the guidelines. When consensus is reached the guidelines are implemented in practice. National guidelines are revised on a regular basis or when new evidence of indications for change in clinical practice is noted.

The increased adherence to national guidelines has led to reduced prescribing of antibiotics, trends towards better antibiotic choices with more narrow spectrum antibiotics and more correct use of patient near testing, such as Strep-A test.

The experts writing and reviewing the guidelines must also consider the risk of under-prescribing and monitor incidences of complications. Incidences of acute mastoiditis have been followed via a prospective study on hospital register of mastoiditis 2008-2017. However, since there are differences in how the diagnosis is made, a validation of the mastoiditis diagnosis in each case is an even better evaluation of the mastoiditis incidence [53]. Other complications, such as peritonsillitis, abscesses, sinusitis, must be monitored via the national register of diagnosis in hospital care. Between 1995-2004 no increase was seen for these diagnoses [52]. New studies to evaluate risk of complications are under way [103].

When there was an increase in serious infections by Group A beta-haemolytic streptococci (GAS) in Sweden, concerns were raised by hospital physicians [47,104]. However, the increase was predominately in patients aged 65 and older. In the debate that followed, the guideline experts found that the most virulent GAS infections causing serious necrotizing fasciitis (NF) and streptococcal toxic shock syndromes (STSS) seldom were preceded by a throat infection but more often by

skin- and soft tissue infections. More often a bacteraemia caused by GAS did not present with any initial local symptoms [105–107]. Hence, the conclusion was that increasing treatment of sore throat in primary care would not prevent the serious invasive streptococcal infections caused by GAS.

These Swedish findings were also supported by studies in the UK, which showed that predictors of complications for acute sore throat could not be identified via patient history or examination. GPs must rely on strategies such as safety netting to lower the risk of complications [108]. The latest Cochrane review on antibiotics for sore throat (based on studies mostly from the 1950s) conclude that antibiotics reduced the risk of complications including peritonsillitis but number needed to treat to benefit were high in high income countries. They found that antibiotics shortened the duration of symptoms by about 16 hours overall [51]. More recent studies conclude that the major suppurative, complications, such as peritonsillitis, AOM, sinusitis and cellulitis, occur in about 1% of patients with acute sore throat regardless of whether given antibiotics or not [109,110].

Consultation rates for RTIs

The national guidelines are intended to constitute a support in the daily clinics of a physician. A helping tool in the diagnostic process as well as a support when abstaining from antibiotic treatment is an option. Informing the patient about the benefits and harms of different treatment options and when to contact health care again is important for good quality practice. Educating the patient during the consultation probably plays a part in the reduction in consultation rates for RTIs.

In **Paper I** we noted a decrease in the number of consultations for RTIs during the years 2008 to 2013. Swedish studies from the mid-1990s have noted the same trend indicating an increased public awareness [45,46]. Public campaigns by Strama and the on-going debate in media have most likely increased the knowledge about antibiotic resistance. The telephone triage performed by nurses at the PHCCs in Sweden probably plays an essential role in the reduction in consultations for RTIs. The nurses are well informed and up-dated on the national guidelines and give important self-advice to patients over the phone. Many patients consult the website www.1177.se (an extensive guide about all medical concerns) where recommendations regarding common infections in primary care are based on the national guidelines.

Antibiotic prescription rates for RTIs

In **Paper I** we found that the variation in antibiotic prescribing between different PHCCs increased for the diagnoses acute bronchitis and acute sinusitis over the years 2008-2013. Some PHCCs improved their prescribing substantially while others did not change at all. The results indicate remaining inappropriate antibiotic prescribing in some PHCCs. We believe all GPs would benefit from regular feedback on their prescribing by means of diagnosis-linked prescription data, in order to reduce these differences and improve antibiotic prescribing.

The optimal monitoring of trends in antibiotic prescribing would be a national register with diagnosis-linked prescribing data covering every PHCC in the country. The PRIS database was the second best as it was the largest such register in Sweden.

European quality indicators

Comparing antibiotic prescribing internationally is made difficult by the differences in how infections are being labelled and the different diagnoses systems used. One way to get around these differences would be to aggregate diagnoses into diagnostic groups and look at the total antibiotic prescribing per group. Another important point is to always define a common denominator, for example antibiotic prescriptions per 1000 patients and year (PY).

In **Paper II** we concluded that percentage prescribed antibiotic per diagnosis is not a useful quality indicator, without considering the consultation incidence for the particular diagnosis. Since a high prescribing percentage and a low consultation incidence could, for a particular diagnosis, result in the same number of prescriptions per 1000 PY as a low prescribing percentage with high consultation incidence. This phenomenon was demonstrated for the diagnosis AOM whereby the Netherlands had a low prescription percentage but high consultation incidence and Sweden the other way around and it resulted in the same number of prescription per 1000 PY. We, therefore, recommend number of prescriptions per 1000 PY per diagnosis as a quality indicator.

Furthermore, regarding choice of antibiotic treatment consideration of national guidelines are essential since a European consensus is not valid in every country. Phenoxymethylpenicillin (Penicillin V) for RTIs is, for example, only recommended in the Scandinavian countries. Furthermore, Pivmecillinam, which is one of the first line treatments for UTIs in Sweden, is not a registered alternative in many European countries.

The European Surveillance of Antimicrobial Consumption (ESAC) organisation has invested much time and effort to develop the European APQIs through a thorough Delphi process [62]. In **Paper II** we made the first practical evaluation of their validity. The evaluation was based on anonymous routine healthcare data and should therefore be possible to use in every day clinical praxis.

Previous attempts to compare antibiotic prescribing between countries have used prescription figures from national reimbursement data, measuring Defined Daily Doses (DDD) per 1000 inhabitants without having access to diagnoses [2,111]. The ESAC project has compared 33 European countries regarding the DDD per 1000 inhabitants per day (DID) for different antibiotics and also seasonal variation as quality indicators [112]. The Antibiotic Prescribing Quality Indicators (APQIs) were an attempt to compare more specific data on quality in antibiotic prescribing, by taking into account the indication for prescribing [62].

Happy audit was another study method comparing antibiotic prescribing between countries [84]. GPs in six different countries registered their consultations for infections regarding symptoms, patient near tests and treatments. They found international variations regarding patients' requests for an antibiotic, most likely due to differences in severity of symptoms, which in turn is depending on patients' threshold to seek healthcare. Audit registrations are associated with the risk of selection bias as the GPs participating are likely to represent a more motivated group of GPs and this may underestimate the antibiotic prescription rate. Furthermore, there is always the risk that only the more correct patient managements are registered, which may also contribute to an underestimation of the problem.

Cultural differences regarding health care also produce challenges when comparing quality in antibiotic prescribing [113,114]. Referring to Figure 8 in the results section we notice that the cause for consulting differ between the three countries so that in Belgium it is more common to consult for URTIs and acute bronchitis, in the Netherlands for acute sinusitis and cystitis and in Sweden for acute tonsillitis and pneumonia. Some of the differences may be explained by the missing data. Furthermore, pneumonia is not treated in primary care in Belgium and the Netherlands, which explains their low consultation incidences. We also speculate that the availability of Strep A RADT test in Swedish PHCCs stimulate to consult for sore throat.

Europeans vary in their knowledge about antibiotics and resistance, with the highest level of knowledge in Finland, the Netherlands and Sweden. [115]. In Sweden, 60% of the antibiotics used in outpatient care are prescribed in primary care while in most other European countries this figure is about 80%.

Resistance in primary care populations

Since the beginning of the 1990s, when the problem with increasing resistant pneumococci was acknowledged, the prevalence of PNSP (MIC≥0.125 mg/L) has decreased and was low among healthy toddlers [17]. Carriage rate of pneumococci was 42% in child-care institutions and prevalence of PNSP (MIC≥0.5 mg/L) was 5% [116]. Prevalence studies in childcare institutions must always consider cluster effects. Carriage rate and transmission of bacterial clones may be higher in childcare groups and may give higher prevalence figures than would be expected in other populations [117,118].

Other European prevalence studies of bacterial resistance in primary care have based their data on mixed populations from primary care as well as patients seeking health care at emergency clinics in hospitals [119–124]. To our knowledge, **Paper III** is the first study on prevalence of resistance in a strict primary care population regarding respiratory tract pathogens.

The Swedish national guidelines recommend Penicillin V as the first line treatment in RTIs when antibiotics are indicated. But, the actual resistance level in primary care populations has not been known. Some concern was raised due to rising levels of PNSP, from 4% in 1997 to 8% in 2010, in the routine data from the microbiological laboratories [125]. The findings in our study of low resistance in pneumococci (6% PNSP, with low MIC) from **Paper III** confirm that Penicillin V can still be used as empirical treatment for RTIs if antibiotics are required.

We know that the ecological coexistence of microbes is constantly evolving and requires regular monitoring. For example we see an increase in nontypeable *H.influenzae* since the introduction of vaccination 1993 [126] and also the proportion of beta-lactam resistant *H.influenzae* in invasive isolates have increased the last decade [127]. Among other developments, the beta-lactamase production in *Moraxella Catarrhalis* has changed from being uncommon before 1975 to 97% prevalence today. *M.catarrhalis* is in many infections coexisting with other pathogens such as *S.pneumoniae* and *H.influenzae* and there are theories that the beta-lactamase production of *M.catarrhalis* protects the other two pathogens from beta-lactam antibiotics [128].

There may be cluster effects involved since the children recruited in our study originated from a more limited geographical area while swabs analysed in the local microbiological laboratory come from the whole region of Scania (1 million inhabitants).

In **Paper III** we saw an increased OR for resistant bacteria in children that had received antibiotics four weeks prior to the swab. This finding is supported by previous studies [69,129–132]. The finding is a reminder to always consider

development of resistance as an adverse effect in every case when antibiotics are used. Even narrow spectrum Penicillin V contributes to the antibiotic pressure among the general population, although this has not been shown.

Furthermore, we found that boys had a higher OR for carrying resistant bacteria, which is supported by a previous study [133] but not by another [131]. Boys have also been shown to catch more RTIs in younger ages than girls [134,135] and develop complications to AOM more often [136]. The reasons for these differences between the sexes are not known.

Since we collect relatively few cultures in primary care, an important reason to investigate the resistance level in the population would be when we notice high resistance figures from the local microbiological laboratory.

Guideline characteristics related to GPs' stated adherence

Clinical guidelines have been seen to improve medical practice and clinical outcomes [137]. Guideline characteristics have been found to have an effect on adherence to guidelines [74]. Moreover, adequate implementation strategies, as well as correct use of language in the guidelines, are important in order to gain acceptance with the users of the guidelines [138,139]. When we explored GPs' stated adherence in relation to guideline characteristics we found that if guidelines are not compatible with GPs' existing norms, the adherence might be low regardless of all the other attributes found to be of importance for adherence to guidelines. The effect was seen particularly for the tonsillitis guidelines, where the principles in the diagnostic process have changed. Previously, the focus was on differentiating whether the condition was caused by virus or bacteria, while the revised guidelines aim to identify which patients are most likely to benefit from antibiotic treatment. We believe that a more thorough implementation program is needed for guidelines that are less compatible with existing norms. Evidence supporting the recommendations should be made easily accessible in connection to the short/pocket version of the guidelines. Furthermore, more focus should be given during the outreach visits by Strama personnel to discuss controversial recommendations in peer review groups [75].

Considering the results from **Paper IV,** we argue that a survey of current norms and values among end-users should be part of the preparatory work when revising or creating clinical guidelines. This suggestion is in line with previous findings [140].

Conclusions and further directions

The strength of the thesis is that it addresses several aspects of quality in antibiotic prescribing in primary care. Current prescribing patterns in Sweden, international outlooks, effects on resistance as well as the prescribers' views are described. Both qualitative and quantitative measures have been used to analyse data.

The thesis has added an overview of the current antibiotic prescribing in Swedish primary care. In **Paper I** we have presented an analysis of diagnosis-linked prescription data on a larger scale, giving directions for further work to reduce antibiotic prescribing. The next step would be to make available diagnosis-linked antibiotic prescription data to all physicians in Sweden, on a regular basis. The format of data presented in **Paper I** corresponds to the quality parameters in the MIRA-project and could be used to monitor quality in antibiotic prescribing when the data is available.

Moving ahead with evaluation of quality indicators for antibiotic use on an international level has proven to meet challenges and in **Paper II** we present factors that need to be addressed for further development of these. International collaboration regarding antibiotic prescribing is important as travelling between countries both for leisure and medical treatment is becoming more and more common, and increases the risk of spreading resistant bacteria.

Showing a low prevalence of resistant bacteria in a strict primary care population in **Paper III** supports current Swedish recommendations for empirical treatment for children with RTIs. Since, rather few cultures are performed on a regular basis in primary care microbiological trends seen in the local laboratory might need further investigation in the respective population before considering possible changes in the guidelines, as a measure of quality.

From interviews with GPs in **Paper** IV, we found that lingering conceptions need to be addressed in the clinical guidelines especially when guideline directions interfere with the doctors' diagnostic process and are in conflict with existing norms. Investigating GPs' views and attitudes to guidelines is advisable prior to creating or revising national guidelines in order to address possible lingering conceptions or other potential barriers to adherence. We regard adherence to guidelines as a measure of quality and good medical practice.

Sammanfattning på svenska

Antibiotikaresistens beräknas av WHO att gå om cancer och trafikolyckor som den ledande dödsorsaken år 2050. Man ser redan nu att bristen på verksamma antibiotika orsakar ca 25 000 dödsfall bara i Europa. I Sverige uppskattas resistenta bakterier orsaka en merkostnad av 5 miljarder för svensk sjukvård fram till 2024, enligt beräkningar från Folkhälsomyndigheten.

Flera aktörer påverkar utveckling och spridning av resistens; läkemedelsindustrin, sjukvården, veterinärvården, djur- och jordbruket, och livsmedelsindustrin. Inom den moderna sjukvården är man helt beroende av att antibiotika är verksamt, bland annat för behandling av invasiva infektionstillstånd, cancerbehandlingar, organtransplantationer och vid de flesta andra kirurgiska ingrepp.

I svensk sjukvård fördelar sig antibiotikaanvändningen ungefär så att inneliggande patienter på sjukhus konsumerar 10 % och i öppenvården förskrivs 90 %. I öppenvården ingår mottagningsverksamhet på sjukhusen, privata specialistmottagningar, tandvård och primärvård. Primärvården står för drygt 60 % av förskrivningen i öppenvården. Det är därför viktigt att rikta åtgärder mot onödig antibiotika användning mot primärvården.

I avhandlingen granskas olika aspekter på antibiotikaförskrivning för att få en helhetsbild, med kartläggning av hur den aktuella förskrivningen ser ut i svensk primärvård, hur vi kan jämföra antibiotikaförskrivning med andra länder och hur resistensläget ser ut bland barn med symtom på luftvägsinfektion. Även en analys av hinder för distriktsläkarnas följsamhet till de nationella riktlinjerna för antibiotikaförskrivning görs.

Delarbete I:

För att veta hur vi kan minska antibiotika användningen i primärvården behöver vi veta hur förskrivningen ser ut idag. Hittills har våra kunskaper baserats på apoteksdata med information om vilka antibiotika som hämtats ut på recept, men vilken diagnos det är riktat mot har inte varit känt. Att få ta del av diagnoskopplade förskrivningsdata har varit ett starkt önskemål från många förskrivare. 2007 upprättades ett register som kallas Primärvårdens

Infektionsdatabas (PRIS) som samlar in diagnoskopplade data från ca 90 vårdcentraler och över 700 000 patienter i Sverige. Dessa data har sammanställts i den första studien. En analys av trender över åren 2008-2010-2013 är gjord med avseende på antibiotikaförskrivning och följsamhet till nationella riktlinjer för antibiotikaförskrivning. Vi såg att både konsultationsfrekvensen och antibiotikaförskrivningen för luftvägsinfektioner minskade, men att den för urinvägs- och hud- och mjukdelsinfektioner var väsentligen oförändrad under den studerade perioden. Vi såg en ökad följsamhet till diagnos- och behandlingsriktlinjerna för öroninflammationer, halsfluss och luftrörskatarr. Men, fortfarande noteras att antibiotikaförskrivningen varierar stort mellan olika vårdcentraler och att fortsatta insatser för en minskad förskrivning är motiverade.

Delarbete II:

Onödig antibiotkaförskrivning är ett globalt problem och det finns anledning att samarbeta internationellt kring dessa frågor. Det skulle därför vara till nytta om vi kunde jämföra mellan länder hur vi förskriver antibiotika. Diagnosbaserade kvalitetsindikatorer har utarbetats av en europeisk expertgrupp inom ramen för ett internationellt samarbete, kallat European Surveillance of Antimicrobial Consumption Network (ESAC-Net). I den andra studien har dessa kvalitetsindikatorer utvärderats genom att jämföra diagnoskopplade förskrivningsdata för sju olika diagnoser från Belgien, Holland och Sverige. Vi fann att det var svårt att jämföra internationella data då det finns stora skillnader mellan länderna med avseende på sjukvårdens organisation, tradition hos invånarna för när man söker läkare, tillgänglighet på sjukvård etc. Vår bedömning var att kvalitetsindikatorerna kan fungera som vägledande, men att de behöver utvecklas vidare och då ta hänsyn till den lokala konsultationsfrekvensen för respektive diagnos och varje lands egna nationella behandlingsriktlinjer.

Delarbete III:

Vi vet att en stor andel av antibiotikaförskrivningen i Sverige sker i primärvården. Barn med luftvägsinfektioner har hittills varit den patientgrupp som fått mest antibiotika förskrivet. Kopplingen mellan antibiotikakonsumtion och bakteriell resistens är dokumenterad i flera vetenskapliga arbeten. Men, vi vet inte hur det ser ut med den bakteriella resistensen i en primärvårdspopulation eftersom nuvarande mått på resistens baseras på mikrobiologens laboratoriedata. Laboratorierna i sin tur baserar mätningarna på odlingar från både inneliggande

patienter och patienter som söker på sjukhusets mottagningar och från vårdcentraler. I den tredje studien samlade vi in 340 odlingar från näsans bakre delar (nasofarynxodlingar) på barn som sökte på vårdcentraler i Skåne med symtom på luftvägsinfektion och fick på så sätt odlingar från en renodlad primärvårdspopulation. Odlingsresultaten visade på en låg förekomst av resistens, och vi kan således hålla fast vid de aktuella behandlingsrekommendationerna med vanligt penicillin V om antibiotikabehandling anses nödvändig. Eftersom befolkningsunderlaget vid rutinmässiga laboratoriemätningar av resistens skiljer sig något från den i primärvården kan det vid en eventuell ändring i resistensläget i laboratoriedata vara av vikt att verifiera den i en primärvårdspopulation innan ändringar i behandlingsrekommendationer företes. Vidare, fann vi att barn som nyligen behandlats med antibiotika oftare hade resistenta bakterier vilket också visats i tidigare studier. Resultatet stödjer det fortsatta arbetet att noggrant välja ut de patienter som har nytta av antibiotikabehandling i primärvården.

Delarbete IV:

Mycket tyder på att nationella diagnos- och behandlingsriktlinjer har betydelse för att minska onödig antibiotikaförskrivning. För att utforma riktlinjerna på bästa möjliga sätt krävs att man vet hur användarna ser på dem och vilka egenskaper som ger bästa följsamhet. Vi analyserade de nationella riktlinjerna för tre vanliga infektioner i primärvården, nedre luftvägsinfektion, öroninflammation och halsfluss, med utgångspunkt från i litteraturen etablerade egenskaper. Vi fann att de tre riktlinjerna hade olika egenskaper som sannolikt påverkar deras följsamhet. Den faktor som visade sig ha stor betydelse för följsamheten var huruvida riktlinjen var i samklang med existerande normer. Vi analyserade också 29 intervjuer med läkare i primärvården. Det framkom att läkarens kvarvarande föreställningar gällande handläggning av infektionspatienter var avgörande för följsamheten. Vi kunde slå fast att det krävs att man vid sammanställning och revidering av nationella riktlinjer bör ta hänsyn till läkarnas etablerade föreställningar kring diagnos och behandling och bemöta dem för att få en god följsamhet.

Patientnytta:

I avhandlingen har vi identifierat förbättringsområden för antibiotikaförskrivning till patienter i svensk primärvård. Återkommande granskningar av diagnoskopplade förskrivningsdata och återkoppling till förskrivare är avgörande

för att vi ska kunna förbättra antibiotikaförskrivningen i framtiden. Vidare har vi dragit viktiga slutsatser kring kvalitetsindikatorers utformning för framtida internationella jämförelser av antibiotikaförskrivning i primärvård.

En aktuell mätning av förekomst av resistens bland luftvägspatogener har kunnat bekräfta att penicillin V är brukbart vid behov av antibiotika till barn med luftvägsinfektion i primärvård. Studier baserade på primärvårdspopulationer behövs innan till exempel behandlingsriktlinjer ändras på grund av fynd baserade på data från mikrobiologiska laboratorier, då resistensdata kan skilja sig åt.

När det gäller nationella diagnos- och behandlingsriktlinjer måste vi bemöta läkarnas kvarstående föreställningar när det gäller handläggning av infektionspatienter i primärvården, annars kan dessa orsaka att riktlinjerna inte följs. Lämpligt vore att inför revidering av nationella riktlinjer göra en undersökning av läkarnas inställning och förförståelse av riktlinjerna i ämnet för att kunna förbättra dem och få en god följsamhet.

Acknowledgement

There are many people I owe great thanks for support during the assembling of this thesis. I would like to direct special thanks to:

Sigvard Mölstad, my supervisor 2013-2016. Sigvard has provided inspiration through his dedicated work with Strama and research in infections in primary care. He has given excellent support and encouragement in the research process. By giving me opportunities to present my research in an international environment, such as in the Baltic Primary Health Care Network, the interregional research group in Copenhagen and the European network GRIN I have achieved new research connections. The network, among other things, led to a research visit (pre-doc) at Bond University in Australia in 2016.

Katarina Hedin, my supervisor in 2016-2017, and role model, who has supported me at all times. Katarina has provided continuous encouragement and guidance in the scientific world and valuable discussions about infections and antibiotics. Both Sigvard and Katarina travelled all the way to Australia during my pre-doc to provide supervision and support.

Anders Beckman, for help with statistical analysis and technical support.

Eva Melander, for support and expertise in respiratory tract pathogens and important forerunner in the subject of antimicrobial resistance and particularly, pneumococci.

Kerstin Troein for invaluable administrative support.

Sven Engström and Christina Lannering in Jönköping for providing data and introducing me to the PRIS database.

My fellow co-authors in the qualitative study; Malin André, Hedvig Gröndal, Annika Brorsson and Eva-Lena Strandberg who guided me in the world of qualitative research.

All teachers at the National Research School in General Practice for excellent guidance and inspiration.

Professor Chris DelMar, my supervisor at Bond University, for showing great interest in my work and introducing me to Australian Primary health care.

Ann-Christine Petersson, head of the microbiological laboratory in Lund, for cooperation's regarding the nasopharyngeal cultures.

Bertil Kjellberg at CPF for graphic support with figures and tables.

My fellow PhD students (in room 28 11031B) and role models; Helena, Cissi, Beata, Moa and Carin.

Head of Lundbergsgatans Vårdcentral, Pia Viktor Persson and all personnel for being understanding at times of my absence from the clinic.

Personnel at all the PHCCs collecting samples for my project, especially my GP colleagues, personnel in the reception and laboratory at Lundbergsgatans Vårdcentral.

The South Swedish Regional Council, and Lund University for financial support.

All good friends who make me think of other things than research.

Special thoughts to my parents for always helping me and for being positive and supportive in all I do.

To Nico and our children Léon, César and Élise, for being patient with me in moments of stress, and for your love.

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Paper I

Tyrstrup et al. BMC Infectious Diseases (2016) 16:709
DOI 10.1186/s12879-016-2018-9

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Reduction in antibiotic prescribing for respiratory tract infections in Swedish primary care- a retrospective study of electronic patient records

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Abstract

Background: Swedish studies on antibiotic use in primary care have been based on one-week registrations of infections. In order to study adherence to guidelines, analyses based on large databases that provide information on diagnosis linked prescriptions, are needed. This study describes trends in management of infections in Swedish primary care particularly with regards to antibiotic prescribing and adherence to national guidelines.

Methods: A descriptive study of Sweden's largest database regarding diagnosis linked antibiotic prescription data, the Primary care Record of Infections in Sweden (PRIS), for the years 2008, 2010 and 2013.

Results: Although the consultation rate for all infections remained around 30% each year, antibiotic prescribing rates decreased significantly over the years from 53.7% in 2008, to 45.5% in 2010, to 38.6% in 2013 ($p = .032$). The antibiotic prescribing rate for respiratory tract infections (RTIs) decreased from 40.5% in 2008 to 24.9% in 2013 while those for urinary tract infections and skin and soft tissue infections were unchanged. For most RTI diagnoses there was a decrease in prescription rate from 2008 to 2013, particularly for the age group 0–6 years. Phenoxymethylpenicillin (PcV) was the antibiotic most often prescribed, followed by tetracycline. Tonsillitis and acute otitis media were the two RTI diagnoses with the highest number of prescriptions per 1000 patient years (PY). For these diagnoses an increase in adherence to national guidelines was seen, with regards to treatment frequency, choice of antibiotics and use of rapid antigen detection test. The frequency in antibiotic prescribing varied greatly between different Primary Healthcare Centres (PHCCs).

Conclusion: Falling numbers of consultations and decreased antibiotic prescription rates for RTIs have reduced the antibiotic use in Swedish primary care substantially. Overprescribing of antibiotics could still be suspected due to large variability in prescribing frequency, especially for acute bronchitis and sinusitis. Continuous evaluation of diagnosis linked prescribing data and feedback to doctors is essential in order to achieve a more prudent antibiotic use.

Keywords: Antibiotic prescribing, Electronic patient records, Family practice, General practice, Primary healthcare, Respiratory tract infections

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Background

Antibiotic use is associated with the development of antimicrobial resistance [1–6]. It has been estimated that 25,000 people die in Europe each year due to resistant bacteria and there are substantial costs associated with prolonged medical treatment time [7]. Negative effects on the environment are also seen, as high levels of resistant bacteria have been found in rivers contaminated with antibiotic substances [8–11]. Together with agriculture and animal production for food, the medical profession has a great responsibility to reduce the antibiotic consumption globally [12].

The frequency of antibiotic prescribing varies greatly between countries in Europe [13–17]. In Sweden 90% of the antibiotics are prescribed in out patient care, of which some 65% are prescribed in primary care, 25% in hospital outpatient department and outpatient department other than primary care, 8% in dental care.

Respiratory tract infections (RTIs) represent the majority (50–60%) of all infections in Swedish primary care and therefore are at focus for efforts to optimise antibiotic prescribing [18, 19] Media campaigns to the public and structured implementation of new guidelines regarding RTIs have been performed on a national basis. Many years of structured work by the Swedish strategic programme against antibiotic resistance (Strama) has significantly reduced the antibiotic use over the last decade [18, 20]. However, the variation in antibiotic prescribing rates between regions and between different practices indicates that there is still probable overprescribing [21, 22].

Within the last ten years, national guidelines regarding Lower Respiratory Tract infections (LRTIs), acute otitis media (AOM) and tonsillitis have been revised and all recommend a more restrictive use of antibiotics than earlier versions. The guidelines for LRTIs were revised in 2007 and they recommend Phenoxymethylpenicillin (PcV) as first line treatment for pneumonia and to abstain from antibiotics in acute bronchitis. When in diagnostic uncertainty, a C-reactive protein (CRP) test could be used. Guidelines for AOM (revised in 2010) recommend wait and see for three days and no immediate antibiotic treatment in children 1–12 years of age without complicating factors. The guideline for tonsillitis (updated in 2012) require the presence of 3 out of 4 Centor criteria (fever ≥38.5 tender cervical adenopathy, purulent tonsils and the absence of cough) and a positive rapid antigen detection test for Beta-haemolytic Streptococcus group A (RADT-Strep-A) before antibiotic treatment is initiated.

Gathering and analysing data on management of patients with infections in primary care forms an essential knowledge-base in order to identify new strategies for prudent antibiotic use. In Sweden, prudent use of antibiotics is defined as prescribing in adherence with current guidelines.

Previous Swedish studies on antibiotic use in primary care have been based on one-week registrations of infectious disease and therefore have included few data [23, 24]. Data from electronic medical records have provided valuable information on antibiotic prescription for upper respiratory tract infections in Sweden [25, 26]. In order to study adherence to guidelines, analyses based on large databases that provide information on diagnosis linked prescriptions, are needed in Sweden.

In 2007 the Primary care Record of Infections in Sweden (PRIS) was introduced. PHCCs were invited to participate on a yearly basis and contribute with data on consultations with an infectious diagnosis and all antibiotic prescriptions. In PRIS the majority of antibiotic prescriptions can be linked to a particular diagnosis, as can information on age, gender, results of CRP and RADT-Strep-A, if applicable, for each patient encounter. Preliminary results have shown a very variable prescription rate as well as variable adherence to guidelines [18, 27].

The aim of this study was to describe how antimicrobials were used in Swedish primary care, 2008–2013. We aim to identify trends over time, particularly for respiratory tract infections with regard to antibiotic prescriptions and adherence to national guidelines.

Methods

This retrospective, descriptive study was based on the information retrieved from the PRIS register, from the years 2008, 2010 and 2013.

The study population

The number of Primary Healthcare Centres (PHCC) contributing data was 47 in 2008, 58 in 2010 and 88 in 2013. In Sweden there were about 1200 PHCCs in total in 2010. In a typical PHCC in Sweden there are about 3–10 General Practitioners working. Together, the PHCCs represented in PRIS, served 460,529 registered patients in 2008 and 785,070 in 2013, of all ages, in both urban and rural areas of Sweden. Accordingly, the number of registered patients in 2013 represented 8% of Sweden's total population of 9,644,864 inhabitants in 2013 [28]. Due to the large number of registered patients in the material the number of patients in each age group was assumed to correspond to the total inhabitants of Sweden as of December 31, for respective year [28].

For each year all registered contacts were traced either due to the presence of an infectious diagnosis according to the International Classification of Disease and Related Health Problems- Tenth Revision (ICD-10), introduced by the WHO, or because an antibiotic prescription by Anatomical Therapeutic Chemical Classification (ATC)-code had been registered. The ATC coding system is used to classify drugs to facilitate studies of drug use in Sweden. With each registered encounter information on

the patient's age, sex and if applicable laboratory testing and antibiotic prescription was recorded. Common near patient tests in Sweden are CRP and RADT-Strep-A.

Some patient encounters had more than one registered diagnosis and sometimes an extra symptom diagnosis had been added, such as cough. The diagnoses in PRIS have therefore been ranked, so that the highest ranked is the diagnosis most likely to cause an antibiotic prescription according to clinical practice. Of the most common RTI diagnoses,, pneumonia has the highest rank, followed by AOM, tonsillitis, sinusitis, acute bronchitis, pharyngitis, common cold and symptom diagnoses like cough. If a contact had generated more than one diagnosis only the highest ranked was retained. The same ranking system was used all years.

Data processing

The different diagnoses were divided into four groups according to type of infection; respiratory tract including ear infections (RTI), urinary tract (UTI), skin and soft tissue (SST) and other infections. The latter group consisted of diagnoses found in Chapter A and B of the ICD-code system, including relatively few patients, and some other diagnoses such as diverticulitis, gynaecological-, and sexual transmitted infections.

RTIs were further divided into upper RTIs (URTIs) and lower RTIs (LRTIs). URTIs were organised into groups that share similarities in clinical practice or national guidelines, such as common cold, sore throat, acute otitis media (AOM) and sinusitis. The group of sore throat consisted mainly of tonsillitis but also acute pharyngitis, mononucleosis, quinsy and scarlet fever. AOM was divided into age groups, due to specific Swedish national guidelines regarding children 1–12 years old.

The LRTIs were divided into chronic obstructive disease (COPD), cough, acute bronchitis, pneumonia and influenza as these groups differ with regard to recommended treatment. Nonspecific chronic bronchitis was included in the COPD.

The consultation and antibiotic prescription rates regarding RTIs in Table 2 and the corresponding figures for total consultation and antibiotic prescription in Table 3 differ slightly. This is because there were some differences as to which diagnostic codes were included in each calculation. The arrangement of diagnoses in Table 2 was done in the initial set up of the variables in PRIS. In Table 3 the inclusion of diagnoses was made later, based on a selection of diagnostic codes from ICD-10. The group "no infectious diagnosis" in Table 2 refers to antibiotic prescriptions with non-infectious diagnosis or no diagnosis registered.

In order to calculate the number of antibiotic prescriptions per 1000 patient year (PY) each PHCC provided information on the number of registered patients at their clinic, calculated as a mean for each year. PY refers to the number of registered patients in the participating PHCCs, per year.

In Table 4 variability in antibiotic prescription rate for five common diagnoses (AOM, sinusitis, tonsillitis, acute bronchitis and pneumonia) is presented. Four of the five diagnoses also appear in Table 3, but with different values for antibiotic prescription rates. The figures in Table 4 were calculated on PHCC level and the figures regarding antibiotic prescription rate in Table 3 referred to an individual level.

Data from the 37 PHCCs who participated all three years, with approximately 380,000 registered patients, was compared to that of all PHCCs. Percentage of consultations for infections, prescribed antibiotics and number of prescription per 1000 PY were calculated (Additional file 1).

Statistical method

All analyses were performed using Excel (Microsoft. Microsoft Excel. Redmond. Washington: Microsoft, 2010. Computer Software) and SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0.Armonk, NY: IBM Corp).

For descriptive statistics, proportions and standard deviations were used. Comparisons between proportions of categorical variables in more than two independent groups were performed with the Chi-square test for trend, using an on-line calculator, http://epitools.ausvet.com.au. *P*-values ≤ .05 were considered statistically significant.

Results

The number of PHCCs providing data to the PRIS record increased over the three years we studied. The population they served increased accordingly, as did the number of consultations for all causes. The percentage of consultations due to infection remained about 30% for each year. (Table 1) 60% of the consultations for infections were made by women each year. The total antibiotic prescription rate decreased significantly from 53.7% in 2008 and 45.5% in 2010 to 38.6% in 2013 ($p = .032$). (Table 1) The prescription rates for the 37 PHCCs that participated all years did not differ from the total regarding proportion of consultations

Table 1 Characteristics of the infections disease dataset

	2008	2010	2013
Number of Primary Healthcare Centres (PHCC)	47	58	88
Number of patient years (PY)	460 529	556 192	785 070
Number of consultations (all causes)	662 184	809 964	1 085 829
Consultations due to infections (percentage of all consultations)	210 388 (31,8%)	245 344 (30,3%)	318 976 (29,4%)
Prescribing rate	53,7%	45,5%	38,6%

that rendered an antibiotic prescription or in the number of prescriptions per 1000 PY (Additional file 1).

Consultations for all infections

RTIs, including AOM, was the most common group of infections, representing more than half of the consultations and resulted in the highest number of prescriptions per 1000 PY. UTIs and SST infections were the second and third most common reason for consultation. The prescribing of antibiotics per 1000 PY decreased significantly for RTIs, but remained unchanged for UTIs and SST infections (Table 2).

The frequency of prescriptions without a diagnosis decreased from 22% in 2008 to 13% in 2013. Antibiotic prescriptions with no registered diagnosis could, due to the type of antibiotic prescribed, be allocated to probable RTIs (PcV, amoxicillin, cephalosporin, doxycycline and macrolides) in 53% (2008), 46% (2010), 41% (2013) of the cases and to UTIs (pivmecillinam, nitrofurantoin, trimethoprim and quinolones) in 28% (2008), 29% (2010) and 40% (2013). SST type antibiotics (betalactam resistant penicillin and clindamycine) represented about 20% of the prescriptions with no diagnosis in all three years.

Consultations and antibiotic prescriptions for RTIs

PcV was the most common antibiotic prescribed for RTIs followed by tetracycline. The proportion of PcV increased and all other antibiotic subclasses decreased from 2008 to 2013 (Fig. 1).

The number of consultations as well as the number of antibiotic prescriptions per 1000 PY for the diagnoses common cold, sore throat, AOM and sinusitis decreased simultaneously over the years (Table 3).

Sore throat was comprised of consultations labelled as tonsillitis in about two thirds of the cases, pharyngitis in one third, and one to two percentages each of mononucleosis, scarlet fever and quinsy. This distribution remained the same over the three years.

Tonsillitis was the condition with the highest prescribing rate among the respiratory tract infections. PcV was used in most cases of tonsillitis, with an increasing frequency over the years. The number of patients with tonsillitis who were prescribed antibiotics, without having been tested with RADT-Strep-A decreased from 39.7% in 2008 to 26.9% in 2013. The patients who were prescribed antibiotics, despite a negative RADT-Strep-A test also decreased from 24.7% in 2008 to 13.1% in 2013.

The number of antibiotic prescriptions per 1000 PY for AOM was halved between 2008 and 2013. Children 1–12 years of age comprised about two thirds of the cases of AOM all three years. (Fig. 2) The fraction given no antibiotics increased significantly from 15.4% in 2008 to 27.0% in 2013 ($p = .041$) and the percentage of patients treated with PcV increased from 73.6% in 2008 to 84.5% in 2013. Among children below 1 year of age the number of patients diagnosed with AOM decreased significantly as did the prescribing of antibiotics (Fig. 2).

The consultation rate for pneumonia remained stable over the years. Pneumonia was most often treated with PcV (53.8%). Although the consultation rate for acute bronchitis remained stable from 2008 to 2013, the antibiotic prescription rate decreased from 59.7% in 2008 to 26.2% in 2013. The most commonly used antibiotic for acute bronchitis was tetracycline (54.1%).

Variability in prescribing between PHCCs

The antibiotic prescribing rate per diagnostic group varied between different PHCC. The largest difference between the lowest and the highest prescribing PHCC was found for the diagnoses acute bronchitis and sinusitis. The mean antibiotic prescription rate per diagnoses per PHCC has decreased for all diagnoses between 2008 and 2013, but the standard deviation (SD) as an indicator for variability has increased for all diagnoses except pneumonia (Table 4).

Use of CRP

CRP was analysed in almost one fourth of all consultations throughout the three years. Almost one third (28.5%) of the patients with sore throat diagnosed in 2013 had a CRP taken. Among the lower respiratory tract infections CRP was used most often among patients diagnosed with pneumonia (60.4%) and acute bronchitis (49.4%).

Consultation and prescribing for RTIs in different age groups

The consultation rate decreased for all age groups, except for 65 years and older, from 2008 to 2013. (Table 5) The prescribing of antibiotics decreased in all age groups, with the largest change (54%) in the age group 0–6 years, from 297 to 136 prescriptions per 1000 PY. PcV was the most common antibiotic in all age groups except in the age 65 years and older, where tetracycline was slightly more common.

Discussion

Main findings

The antibiotic prescribing rate for RTIs decreased from 40.5% in 2008 to 24.9% in 2013, while those for UTIs and SST infections were unchanged. All the diagnoses regarding URTIs showed a decrease in both consultation and prescription rate during the years 2008–2013. Figures suggested increased adherence to guidelines for AOM, LRTIs and tonsillitis.

We noted substantial reduction in antibiotic prescribing for acute bronchitis. Increased variability in prescribing rates between different PHCCs was found, particularly for the diagnoses acute bronchitis and sinusitis.

Table 2 Consultations and antibiotic prescribing according to type of infection per 1000 person years (PY), years 2008, 2010 and 2013

	2008			2010			2013		
	Consultations per 1000 PY	Share of all infection consultations (%)	Antibiotic prescriptions per 1000 PY	Consultations per 1000 PY	Share of all infection consultations (%)	Antibiotic prescriptions per 1000 PY	Consultations per 1000 PY	Share of all infection consultations (%)	Antibiotic prescriptions per 1000 PY
Respiratory tract, incl AOM[a]	251	54,9	102	254	57,5	84	227	55,8	56
Skin and soft tissue	49	10,8	31	53	12,0	29	64	15,7	30
Urinary tract	45	9,9	36	50	11,2	38	48	11,9	36
Other infections[b]	36	7,9	3	36	8,1	3	33	8,2	2
No infectious diagnosis[c]	76	16,6	74	49	11,2	48	34	8,3	32
All	457	100	245	441	100	201	406	100	157

[a]Diagnostic group excluding diagnoses in chapter 1 of ICD-code system
[b]Diverticulitis, STI, gynaecological- and viral infections
[c]Prescriptions with non-infectious diagnosis or no diagnosis registered

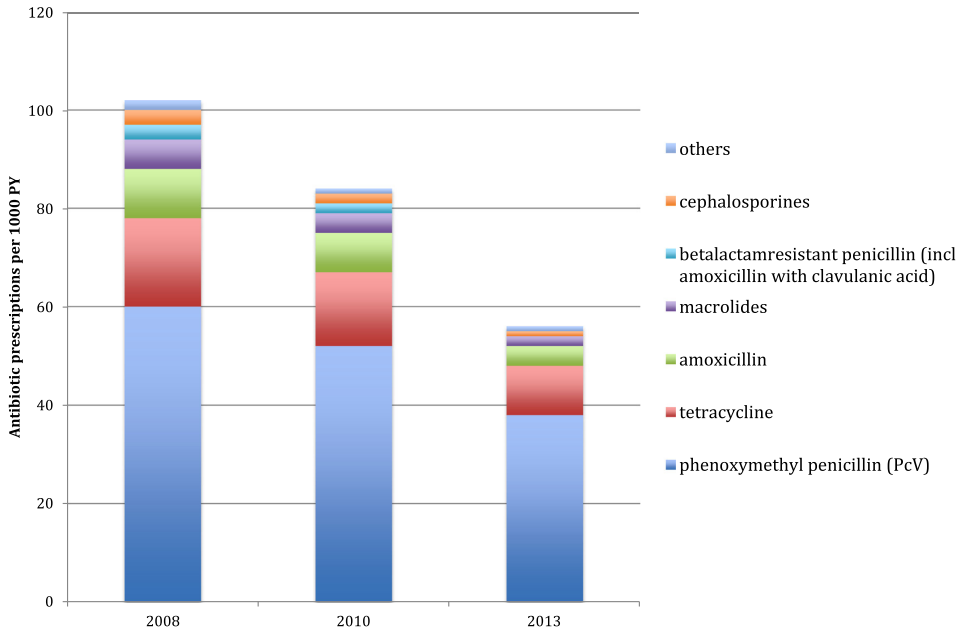

Fig. 1 Trends of antibiotic subclasses for treatment of RTIs in the years 2008, 2010 and 2013

Findings in relation to current guidelines

Overall these findings indicate an increased adherence to guidelines over time. This is reflected in the reduction in the numbers of patients diagnosed with AOM, the increased prescription of PcV in children and the increased rate of treatment with no-antibiotic in children (Fig. 2), and the decrease in antibiotics for tonsillitis and pharyngitis. While it should be noted that the introduction of the pneumococcal vaccine in the general vaccination program in Sweden in 2008–2009 may also have played a part in the reduction of AOM in the age group <1 year. [29, 30], taken together these findings suggest an increased adherence to diagnosis and treatment guidelines.

Furthermore, the antibiotic prescribing rate for acute bronchitis decreased substantially and is approaching the recommended level of less than 20% according to Swedish College of General Practice. The consultation and prescription rates for pneumonia were constant over the three years. Thus, there does not seem to have been a shift in choice of diagnosis from acute bronchitis to pneumonia to explain the decrease in use of antibiotics for acute bronchitis. For all RTIs, except acute bronchitis and COPD the most commonly used substance was PcV, which is in accordance with national guidelines.

However, adherence to guidelines can still be improved since many of the patients treated with antibiotics, with the diagnosis tonsillitis, had no RADT-Strep-A taken or a negative test. Swedish interview studies have indicated that high prescribing doctors were not aware of or not updated on the national guidelines for tonsillitis [31], which may explain the current findings. Finally, excessive use of CRP as a diagnostic tool, was noted, particularly in association with common cold and sore throat, which is not according to guidelines.

Also the increased variability in antibiotic prescription rate per diagnoses between different PHCCs (Table 4) suggests inappropriate antibiotic prescribing. Further analyses as to what factors are important for changing prescribing behaviours are needed.

Previous studies

Our findings indicate a decrease in antibiotic prescribing rate for RTIs. This is in line with previous Swedish studies based on electronic patient records [25, 26] and a diagnosis- prescribing survey [23] performed in the early 2000.

The continuous reduction in consultation rates seen in previous studies as well as in ours could be an effect of the arising debate in media and among the public with a more critical view of the use of antibiotics, which started

Table 3 Consultations and antibiotic prescriptions per 1000 patient years (PY) in different RTI diagnoses, years 2008, 2010, 2013

		2008			2010			2013		
		Consultations per 1000 PY	Antibiotic prescription per 1000 PY	Prescribing rate per diagnosis, (%)	Consultations per 1000 PY	Antibiotic prescription per 1000 PY	Prescribing rate per diagnosis, (%)	Consultations per 1000 PY	Antibiotic prescription per 1000 PY	Prescribing rate per diagnosis, (%)
Upper respiratory tract infections	Common cold	103	12	11,8	101	8	7,8	86	4	4,5
	Sore throat[a]	42	28	67,7	38	23	61,4	29	18	59,7
	AOM[b]	27	23	84,5	24	20	80,6	16	12	74,9
	Sinusitis	17	14	81,0	15	11	70,9	12	7	60,6
Lower respiratory tract infections	Cough	24	2	8,3	30	2	6,5	28	1	4,0
	COPD	11	2	14,5	17	2	11,1	28	2	7,8
	Acute bronchitis	22	13	59,7	22	10	45,4	18	5	26,2
	Pneumonia	10	7	66,2	11	7	61,9	11	7	62,5
	Influenza	2	0,1	6,3	1	0,1	7,4	4	0,1	3,3
Total[c]		258	101		259	83		232	55	

[a]Sore throat comprises the diagnosis tonsillitis, pharyngitis and mononucleosis, quinsy and scarlet fever.[b]Acute Otitis Media (AOM) [c]Total values for RTIs add up to higher values than RTIs in Table 2 due to inclusion of some diagnoses from chapter 1 of ICD-code system

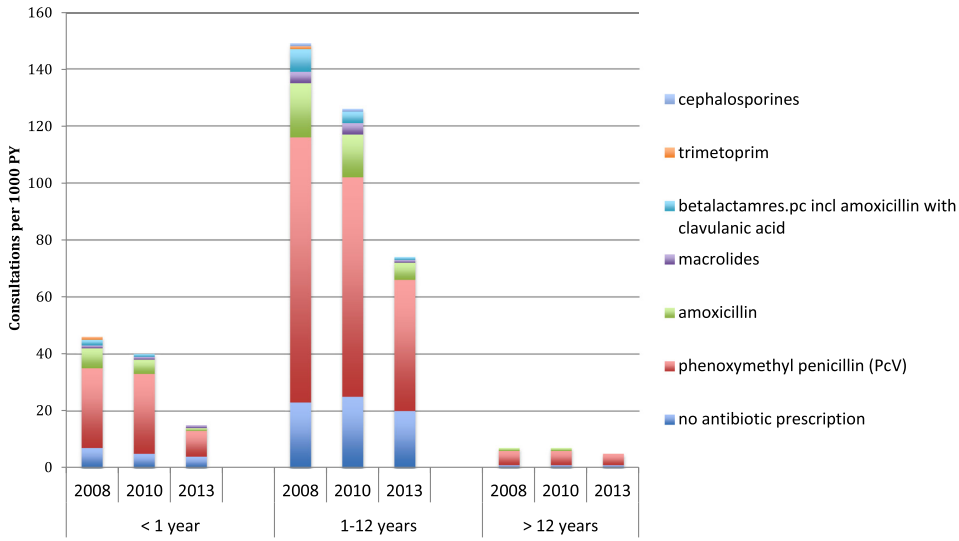

Fig. 2 Trends for treatment of AOM according to age group in the years 2008, 2010 and 2013

in the early 90's. In addition, an increased focus on the health care level with campaigns to reduce antibiotic prescribing by educational efforts towards health professionals and national targets for good practice, may have played a part in the reduction in consultation rates as well as antibiotic prescription rates, as was noted in 2008–2013 [20].

Studies based on large diagnosis linked prescription registers can, among other countries, be found in the United Kingdom (UK) and the Netherlands. In contrast to Sweden, the antibiotic prescribing for coughs/cold is reported to have increased in the UK over the years 1995–2011 despite implementation of national guidelines [32]. The increase seem to be due to an increased consultation incidence for coughs/cold in the UK, which was not seen in Sweden. A possible explanation is the gate-keeping function of the nurse triage. As a rule, to book an appointment with a GP in a Swedish PHCC the patient need to speak to a nurse first. The nurses' triage is performed according to current guidelines and in many cases you will be given enough advice by the nurses at this level and will not need to see the GP. In addition, in Sweden most patients do not need a sick-leave note the first week of illness for themselves or for a sick child. This may explain why numbers of consultations for RTIs are low in Sweden compared to other countries [32, 33].

Table 4 Variability in antibiotic prescription rate between PHCCs, for RTIs commonly treated with antibiotics

	2008 Prescription rate % (SD[a])	2010 Prescription rate % (SD[a])	2013 Prescription rate % (SD[a])
AOM[b]	84.5 (7.9)	79.3 (8.1)	74.4 (8.5)
Sinusitis	80.4 (8.7)	70.6 (12.1)	62.5 (12.7)
Tonsillitis	88.4 (8.0)	83.6 (9.3)	80.0 (10.1)
Acute bronchitis	60.1 (15.5)	45.6 (17.3)	28.2 (17.4)
Pneumonia	66.1 (12.1)	61.1 (12.0)	63.0 (9.7)

[a]Standard Deviation (SD)
[b]Acute Otitis Media (AOM)

In the Netherlands antibiotic prescribing has been rather stable and not decreased between 2007 and 2010 [33]. Antibiotics were prescribed in 26% of infectious disease episode in the Netherlands in 2010 and in 45,5% the same year in Sweden. However, the Dutch recorded more infectious episodes per patient year (1065) compared to what was found in our material (441) for 2010. Again, the gate-keeping function may play a role to keep consultation rates low in Sweden. Similarly, for AOM, the antibiotic prescription rate in the Netherlands was low (45.8%) compared to Sweden (80.6%) in 2010, but since the consultation for AOM per 1000 PY was lower in Sweden (24.3) compared to the Netherlands (38.2) the antibiotic prescription per 1000 PY was rather similar, 20 for Sweden and 17 for the Netherlands. (80.6% of 24.3 = 20 and 45.8% of 38.2 = 17).

Sore throat, including tonsillitis and pharyngitis, is noted to have similar treatment frequencies in the UK (62%), the

Table 5 Consultations and antibiotic prescriptions per 1000 patient years (PY) for RTIs in 2008, 2010 and 2013, for different age groups

	2008		2010		2013	
Age-Group (years)	Consultations per 1000 PY	Antibiotic prescription per 1000 PY	Consultations per 1000 PY	Antibiotic prescription per 1000 PY	Consultations per 1000 PY	Antibiotic prescription per 1000 PY
0–6	712	297	703	254	467	136
7–18	247	109	251	91	171	62
19–64	204	84	200	67	181	47
65-	206	68	228	57	280	48
Total	251	102	254	84	229	56

United States (60%) and Sweden (60%) but a little lower in the Netherlands (55%) [32–34]' The reason for the relatively high consultation rate for sore throat in Sweden is believed to be associated with the high availability of the RADT-Strep A at every PHCC, as well as other factors.

Strength and limitations

The PRIS database contains the largest number of patient registrations with diagnosis linked data on antibiotic prescribing in primary care in Sweden. The PHCCs represented in the database are participating on a voluntary basis, which might cause a selection of more motivated PHCCs and hence, better prescribing rates. On the other hand, the fact that in some of the geographic areas, all of the PHCCs participate contradicts a selection bias. In addition, private and public PHCCs in both rural and urban areas are represented. The number of participating PHCCs increased from 2008 to 2013 and accordingly, the number of consultations, but the percentage related to an infection remained constant (30%), which reduces the likelihood of a very strong selection bias. It can be argued that all calculations should be based only on the PHCCs participating all years, however that would make some of the data less reliable, for example AOM and age groups. We therefore compared the prescription rate and number of prescriptions per 1000 PY for the 37 PHCCs that participated all years with the total and did not find any differences (Additional file 1). In addition, the antibiotic prescription rates for UTIs and SST infections remained unchanged while a reduction was seen for RTIs. This reduction was in line with the revised and implemented guidelines for RTIs (AOM, LRTIs and tonsillitis) during the study period.

According to the Public Health Agency of Sweden the mean total antibiotic prescriptions per 1000 inhabitants in Sweden were 443 in 2008, 406 in 2010 and 343 in 2013 [18]. So, the national data on sale show a reduction of 100 prescriptions per year between 2008 and 2013 and in our study we found a decrease of 88 prescriptions (from 245 to 157). This indicates that our results are in line with trends in national data on antibiotic sales and that most of the reduction in antibiotic use may have taken place in primary care.

A limitation is that no visits after office-hours were included in the register, which could cause an underestimation of the frequency of infections as well as of antibiotic prescribing. Control visits could not be distinguished from a first visit, which might cause overestimation of the number of certain diagnoses such as pneumonia and AOM and hence also underestimation of the percentage of antibiotic prescribing for these diagnoses.

Another limitation is that for 13.5% of the prescriptions there was not a linked diagnosis. The majority (2/3) of these antibiotics were prescribed without a patient visit. Possible explanations are prescriptions for patients at nursing homes, from consultations by telephone or prescriptions being registered later after receiving results from cultures or x-rays.

Conclusion and future directions

This study supports that primary healthcare in Sweden has succeeded to improve prescribing of antibiotics in accordance to national guidelines. Both consultations and and antibiotic prescribing for RTIs have decreased. The significant decrease in prescribing rate for AOM and tonsillitis indicate that updating and implementing national guidelines is an important tool to reduce antibiotic use.

There are still large variations in prescribing frequencies between different PHCCs, indicating that irrational antibiotic prescribing still exists. Continuous evaluation of diagnosis linked prescribing data and feedback to doctors is essential in order to make changes towards more prudent antibiotic use.

Additional file

Additional file 1: Sensitivity analysis. (DOCX 18 kb)

Acknowledgements

We thank the Unit of Research and Primary Care in Jönköping and the Public Health Agency of Sweden, for the support and financial contribution for the PRIS register.

Funding

Construction and maintenance of the database PRIS has been paid for by the County Council of Jönköping with contributions from The Public Health Agency of Sweden."

Availability of data and materials
Data can be shared upon request.

Authors' contributions
SM initiated the study. CL and SE managed the initial gathering of the PRIS dataset. MT carried out the collation and analysis of the data and drafted the manuscript. AB, KH and SE supported in the statistical analysis. EM commented and contributed to the manuscript. All authors critically revised and approved of the final manuscript.

Authors' information
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Confidentiality for patients was ensured by one-way encrypted ID-number. Ethical approval was obtained from the Regional Ethical Review Board in Linköping, Sweden, for the PRIS register (Dnr 2010/227-31).

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Received: 14 October 2015 Accepted: 11 November 2016
Published online: 25 November 2016

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Supplement 1; sensitivity analysis

Table 1. Characteristics of the infectious disease dataset

	2008		2013	
	All	Constant 37	All	Constant 37
Number of Primary Healthcare Centres (PHCC)	47	37	88	37
Number of patient years (PY)	460 529	369 548	785 070	379 338
Number of consultations (all causes)	662 184	513 698	1 085 829	563 107
Consultations due to infections (percentage of all consultations)	210 388 (31.8%)	162 890 (31.7%)	318 976 (29.4%)	153 193 (27.2%)
Prescribing rate	53.7%	51.8	38.6%	38.9
Prescriptions per 1000 patient years	245	228	157	157

Consultation rates and antibiotic prescribing rates were calculated for all participating PHCCs and for the constant 37 PHCCs, participating all three years. Reductions in antibiotic prescribing rate for all PHCCs and for the constant 37 PHCCs were significant, $p<0.01$.

Table 1 Consultations and antibiotic prescribing according to type of infection per 1000 person years (PY), years 2008 and 2013

	2008						**2013**					
	Consultations per 1000 PY		Share of all infection consultations (%)		Antibiotic prescriptions per 1000 PY		Consultations per 1000 PY		Share of all infection consultations (%)		Antibiotic prescriptions per 1000 PY	
	All	*Const.37*	All	*Const.37*	All	*Const.37*	All	*Const.37*	All	*Const.37*	All	*Const.37*
Respiratory tract, incl AOM*	251	*247*	54.9	*55.9*	102	*96*	227	*227*	55.8	*56.2*	56	*59*
Skin and soft tissue	49	*48*	10.8	*10.8*	31	*29*	64	*59*	15.7	*14.6*	30	*28*
Urinary tract	45	*42*	9.9	*9.8*	36	*36*	48	*47*	11.9	*11.7*	36	*34*
All	457	*441*	100	*100*	245	*228*	406	*404*	100	*100*	157	*157*

Consultations and antibiotic prescriptions per 1000 patient per year (PY) were calculated for all participating PHCCs and for the constant 37 PHCCs participating all three years.

Paper II

SCANDINAVIAN JOURNAL OF PRIMARY HEALTH CARE, 2017
VOL. 35, NO. 1, 10–18
http://dx.doi.org/10.1080/02813432.2017.1288680

Taylor & Francis
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RESEARCH ARTICLE

OPEN ACCESS

Antibiotic prescribing in relation to diagnoses and consultation rates in Belgium, the Netherlands and Sweden: use of European quality indicators

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ABSTRACT

Objective: To assess the quality of antibiotic prescribing in primary care in Belgium, the Netherlands and Sweden using European disease-specific antibiotic prescribing quality indicators (APQI) and taking into account the threshold to consult and national guidelines.

Design: A retrospective observational database study.

Setting: Routine primary health care registration networks in Belgium, the Netherlands and Sweden.

Subjects: All consultations for one of seven acute infections [upper respiratory tract infection (URTI), sinusitis, tonsillitis, otitis media, bronchitis, pneumonia and cystitis] and the antibiotic prescriptions in 2012 corresponding to these diagnoses.

Main outcome measures: Consultation incidences for these diagnoses and APQI values (a) the percentages of patients receiving an antibiotic per diagnosis, (b) the percentages prescribed first-choice antibiotics and (c) the percentages prescribed quinolones.

Results: The consultation incidence for respiratory tract infection was much higher in Belgium than in the Netherlands and Sweden. Most of the prescribing percentage indicators (a) were outside the recommended ranges, with Belgium deviating the most for URTI and bronchitis, Sweden for tonsillitis and the Netherlands for cystitis. The Netherlands and Sweden prescribed the recommended antibiotics (b) to a higher degree and the prescribing of quinolones exceeded the proposed range for most diagnoses (c) in Belgium. The interpretation of APQI was found to be dependent on the consultation incidences. High consultation incidences were associated with high antibiotic prescription rates. Taking into account the recommended treatments from national guidelines improved the results of the APQI values for sinusitis in the Netherlands and cystitis in Sweden.

Conclusion: Quality assessment using European disease-specific APQI was feasible and their inter-country comparison can identify opportunities for quality improvement. Their interpretation, however, should take consultation incidences and national guidelines into account. Differences in registration quality might limit the comparison of diagnosis-linked data between countries, especially for conditions such as cystitis where patients do not always see a clinician before treatment.

KEY POINTS

The large variation in antibiotic use between European countries points towards quality differences in prescribing in primary care.

- The European disease-specific antibiotic prescribing quality indicators (APQI) provide insight into antibiotic prescribing, but need further development, taking into account consultation incidences and country-specific guidelines.
- The incidence of consultations for respiratory tract infections was almost twice as high in Belgium compared to the Netherlands and Sweden.
- Comparison between countries of diagnosis-linked data were complicated by differences in data collection, especially for urinary tract infections.

ARTICLE HISTORY
Received 19 March 2016
Accepted 7 October 2016

KEYWORDS
General practice; drug therapy; anti-bacterial agents; quality of health care; evidence-based medicine

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Supplemental data for this article can be accessed here.

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Introduction

Antibiotic use is recognised as the main driver of antimicrobial resistance. Consequently, the overuse of antibiotics unnecessarily induces resistance development [1–3]. The largest volumes of antibiotics are prescribed in primary care, with respiratory and urinary tract infections (RTI and UTI) being the most common indications for prescribing [4,5]. National and European surveillance of antibiotic use provides insight into the overall primary care antibiotic consumption, and into the subtypes of antibiotics used. The surveillance data are based on antibiotic sales statistics from pharmacies and are available as defined daily doses per 1000 inhabitants per day (DID) and for some countries also as number of packages per 1000 inhabitants per day (PID). Research by the European Surveillance of Antimicrobial Consumption project (ESAC), currently known as ESAC-Net, showed large variation throughout Europe with regard to these outcomes, suggesting important quality differences [6,7]. These differences urge for interventions or campaigns to improve the quality of antibiotic use. The available surveillance data, however, do not provide enough guidance to identify national focus areas for interventions, as they do not provide the indication for prescribing.

Patients' antibiotic use is in most cases the result of the following decision-making steps. First, the patient decides to present to primary care: consultation decision. Second, the primary care clinicians [general practitioners (GPs) and nurses] decide whether or not to prescribe an antibiotic: prescription decision. Third, when antibiotics are deemed necessary, the clinician decides what antibiotic to prescribe: subtype decision. Fourth, the patient decides whether or not to collect the prescription, start the treatment and whether or not to complete the treatment: intake decision. In the process of improving the quality of antibiotic use, insight into all of these steps is necessary in order to identify targets for intervention.

The ESAC project proposed a set of 21 disease-specific antibiotic prescribing quality indicators (APQIs) [8]. They are intended to assess the quality of the GPs' prescribing and subtype decision (Steps 2 and 3), i.e. for each of seven diagnoses (upper respiratory tract infection (URTI), sinusitis, tonsillitis, otitis media, bronchitis, pneumonia and cystitis): (a) the percentage of patients prescribed an antibiotic, (b) the percentage prescribed first-choice antibiotics and (c) the percentage prescribed quinolones. For each indicator ranges of acceptable APQI values were proposed based on European consensus (Table 1).

In order to evaluate the APQIs, it is necessary to consider the national guidelines as they might differ in their recommendations from the European consensus [8]. In addition, the consultation incidence may affect the antibiotic prescription rate [8] such that a low consultation incidence with a high prescribing percentage [APQI (a)] can equal a high consultation incidence with a low prescribing percentage in the total amount of prescriptions. We, therefore, present consultation incidences for each diagnosis (Step 1), diagnosis-linked prescription data and the outcomes of the APQIs (Steps 2 and 3) from primary care networks in Belgium, the Netherlands and Sweden.

The aim of this study is to evaluate the feasibility of using routine care data from electronic patient records (EPR) to analyse quality indicators for antibiotic prescribing and to investigate whether the outcomes could guide improvement strategies for antibiotic use in the respective countries.

Methods

Design

We conducted a retrospective observational study of primary care databases from three different countries. Calculation of the APQI values requires databases with information on patients' gender, age, diagnosis and the antibiotic prescribed, with diagnoses labelled according to the revised second edition of International Classification of Primary Care (ICPC-2-R) [9,10] and antibiotic prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification [11]. The study period was 1 year (1 January until 31 December 2012). For each diagnosis, we determined whether or not an antibiotic was prescribed, and which one. For quality and internal validity reasons, we noted the percentage of antibiotic prescriptions not linked to a diagnosis. These were 40% for Belgium, 16% for the Netherlands and 26% for Sweden.

Primary care databases

Belgian data were retrieved from the Intego Network, providing anonymous routine healthcare data (office hours of weekdays) from digital patient records of 51 general practices (94 GPs) located all over the region of Flanders, which all use the same medical record software (Medidoc) (Table 2). More details on the Intego Network were described elsewhere [12,13]. The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven under N° ML1723 and approved

Table 1. List of proposed disease-specific APQIs in Europe.

No.	Title	Acceptable range (%)
1a.	The percentage of patients aged between 18 and 75 years with acute bronchitis/bronchiolitis (ICPC-2-R: R78) prescribed antibacterials for systemic use (ATC: J01)	0–30
1b.	= 1a. receiving the recommended antibacterials (ATC: J01CA or J01AA)	80–100
1c.	= 1a. receiving quinolones (ATC: J01M)	0–5
2a.	The percentage of patients older than 1 year with acute upper respiratory infection (ICPC-2-R: R74) prescribed antibacterials for systemic use (ATC: J01)	0–20
2b.	= 2a. receiving the recommended antibacterials (ATC: J01CE)	80–100
2c.	= 2a. receiving quinolones (ATC: J01M)	0–5
3a.	The percentage of female patients older than 18 years with cystitis/other urinary infection (ICPC-2-R: U71) prescribed antibacterials for systemic use (ATC: J01)	80–100
3b.	= 3a. receiving the recommended antibacterials (ATC: J01XE or J01EA or J01XX)	80–100
3c.	= 3a. receiving quinolones (ATC: J01M)	0–5
4a.	The percentage of patients older than 1 year with acute tonsillitis (ICPC-2-R: R76) prescribed antibacterials for systemic use (ATC: J01)	0–20
4b.	= 4a. receiving the recommended antibacterials (ATC: J01CE)	80–100
4c.	= 4a. receiving quinolones (ATC: J01M)	0–5
5a.	The percentage of patients older than 18 years with acute/chronic sinusitis (ICPC-2-R: R75) prescribed antibacterials for systemic use (ATC: J01)	0–20
5b.	= 5a. receiving the recommended antibacterials (ATC: J01CA or J01CE)	80–100
5c.	= 5a. receiving quinolones (ATC: J01M)	0–5
6a.	The percentage of patients older than 2 years with acute otitis media/myringitis (ICPC-2-R: H71) prescribed antibacterials for systemic use (ATC: J01)	0–20
6b.	= 6a. receiving the recommended antibacterials (ATC: J01CA or J01CE)	80–100
6c.	= 6a. receiving quinolones (ATC: J01M)	0–5
7a.	The percentage of patients aged between 18 and 65 years with pneumonia (ICPC-2-R: R81) prescribed antibacterials for systemic use (ATC: J01)	90–100
7b.	= 7a. receiving the recommended antibacterials (ATC: J01CA or J01AA)	80–100
7c.	= 7a. receiving quinolones (ATC: J01M)	0–5

J01: antibacterials for systemic use; J01AA: tetracyclines; J01CA: penicillins with extended spectrum; J01CE: β-Lactamase sensitive penicillins; J01EA: trimethoprim and derivatives; J01M: quinolone antibacterials; J01XE: nitrofuran derivatives; J01XX: other antibacterials.

Table 2. Country specific data and characteristic of dataset.

Country	Belgium	Netherlands	Sweden
Population in whole country (2012) (source: www.statista.com)	11.1 million	16.7 million	9.6 million
DID[a] (year 2012)	29.8	11.3	14.1
PID[b] (year 2009)	2.53	1.53	1.19
No. of practices in study	46	45	52
No. of GPs in study	94	160	212
Total no. of patients registered with the practices	113 549[c]	266 417	338 149
No. of consultations (diagnosis in study with gender and age limitations)	34 044	55 529	59 534
Total no. of consultations per 1000 PY[d], (diagnoses in study with gender and age limitations)	341	329	243
Total no. of prescriptions per 1000 PY[d] (diagnoses in study with gender and age limitations)	189	170	138

[a]Defined daily dose (DDD) per 1000 inhabitants per day, Reference [6].
[b]No. of packages per 1000 inhabitants per day, Reference [6].
[c]Estimated according to Reference [15].
[d]PY refers to the number of registered patients in the participating practices per year.

compliant with the law according to the Sectorial Committee "Health" of the Belgian privacy commission (decision no. 13.026, 19 March 2013).

Dutch data were retrieved from the Julius General Practitioners Network, providing anonymous routine healthcare data (office hours of weekdays) from digital patient records of 45 general practices (160 GPs) located in the centre of the Netherlands (Table 2). The Julius General Practitioners Network, the extraction and generation of the database were described elsewhere [14]. In the Netherlands, one diagnosis might represent more than one consultation, as consultations for the same ICPC code within a pre-specified time frame combine into one episode.

Swedish anonymised data were retrieved from all 52 general practices (212 GPs and interns/residents) located in Jönköping County (office hours of weekdays), which all use a common medical record (Cosmic), with a universal database (Table 2). More than 95% of all encounters were labelled with an ICD 10 diagnostic code. The required ICD 10 codes were converted into ICPC-2-R codes (see Supplement 1).

Consultation incidence and antibiotic prescriptions per 1000 patient years

The numbers of consultations/episodes coded with the diagnosis under study (ICPC-2-R code) (within age and gender limits) were divided by the numbers of patients (within the same limits) registered at the participating general practices and multiplied by 1000.

For Belgium, the number of registered patients for the general practices was not available. Instead, we used the number of patients contacting their general practice over 1 year (90 839), according to the Intego database, and multiplied by 1.25. The factor of 1.25 has been calculated by comparing national reimbursement data with data from the Intego Network [15].

For each of the seven diagnoses we calculated the number of antibiotic prescriptions per 1000 patient years (PY) by multiplying the number of consultations per 1000 PY (consultation incidence) by the percentage of prescriptions per diagnosis.

Disease-specific APQI

For seven acute infections (URTI, sinusitis, tonsillitis, otitis media, bronchitis/bronchiolitis, pneumonia and cystitis) labelled with ICPC-2-R codes R74, R75, R76, H71, R78, R81 and U71, respectively (see Supplement 1 for the corresponding IDC-10 codes) ESAC proposed three quality indicators: (a) the percentage of patients (within specified age and/or gender groups) prescribed an antibiotic; (b) the percentage of patients (within specified age and/or gender groups) prescribed the antibiotic recommended by the European consensus and (c) the percentage of patients (within-specified age and/or gender groups) prescribed quinolones [8]. For each of the 21 APQIs, a range of acceptable values was proposed (Table 1). The acceptable ranges for (a) the percentage of patients prescribed an antibiotic were 0–20% for URTI, tonsillitis, sinusitis and otitis media, 0–30% for bronchitis and 80–100% for pneumonia and cystitis. The acceptable range for (b) the percentage of recommended antibiotic was 80–100%. For (c) the percentage of patients prescribed a quinolone the acceptable range was 0–5%. The recommended first-choice antibiotic for URTIs and tonsillitis were β-lactamase sensitive penicillins, for acute bronchitis, sinusitis, media otitis and pneumonia penicillins with extended spectrum, and for cystitis, nitrofurantoin or trimetoprim. We compared the country's APQI values with these proposed ranges of acceptable values [8].

Exclusion of one indicator

In a previous study, it was found that the interpretation of Indicator 7a (the percentage of patients receiving an antibiotic for pneumonia) could be hampered due to additional diagnostic investigations and/or hospital referral before starting antibiotic treatment [13]. Therefore, we present the figures for Indicator 7a but excluded them from the overall quality assessment.

Data were analysed using Microsoft Excel 2010 and SPSS version 21 (SPSS Inc., Chicago, IL).

Results

Comparison of consultation incidences

For the seven diagnoses under study consultation incidences varied between Belgium, the Netherlands and Sweden, from 243 to 341 per 1000 registered patients per year (PY) (Table 2). Consultation incidence for the diagnoses URTI and bronchitis in Belgium were twice as high compared to the Netherlands and Sweden (Table 3). In the Netherlands, the consultation incidences of cystitis and sinusitis were higher than in the other countries, while the consultation incidence of tonsillitis in Sweden was twice of that in the Netherlands. High consultation incidences were associated with high numbers of antibiotic prescriptions per 1000 PY per diagnosis (Table 3).

Comparison of quality assessment using APQI

Table 3 shows all APQI values for Belgium, the Netherlands and Sweden. For the 20 APQIs in the analysis, 16, 10 and 9 values exceeded the respective ranges of acceptable values. Using the antibiotics recommended in the national guidelines improved the results of indicator b significantly, from 22 to 82% for sinusitis in the Netherlands and from 41 to 94% for cystitis in Sweden.

In Belgium, more than 60% of patients with bronchitis, tonsillitis, sinusitis or otitis media were prescribed an antibiotic (Indicator a) (Table 3). For none of these diagnoses was the use of recommended antibiotics within the proposed range of acceptable values (Indicator b). For bronchitis, sinusitis, pneumonia and cystitis, quinolone prescribing was higher than the acceptable level of 5% (Indicator c).

The Netherlands deviated the most from the acceptable ranges regarding the percentage of patients receiving antibiotics for cystitis and the choice of antibiotics for sinusitis.

More than 45% of patients with sinusitis, tonsillitis, otitis media or bronchitis were prescribed an antibiotic (Indicator a) (Table 3). For most of the indications, the use of the recommended antibiotics was within or close to the proposed range of acceptable values. The largest deviations from the acceptable ranges were observed for the treatment of URTI and sinusitis (Indicator b). Only for cystitis was the 5% upper limit of acceptable quinolone prescribing exceeded (Indicator c).

Table 3. Values for APQIs according to age and gender limits.

Diagnostic code[a]	R74				R75				R76				H71				R78				R81				U71			
Diagnoses in text	Upper respiratory infection acute				Sinusitis acute/chronic				Tonsillitis acute				Acute otitis media				Acute bronchitis/bronchiolitis				Pneumonia				Cystitis/urinary infection other			
Population (age group)	>1 years				>18 years				>1 years				>2 years				18–75 years				18–65 years				Female >18 years			
Country	BE	NL	SE		BE	NL	SE		BE	NL	SE		BE	NL	SE		BE	NL	SE		BE	NL	SE		BE	NL	SE	
Consultation incidence[b]	190	75	66		22	35	16		20	14	28		18	22	14		43	17	22		3	10	16		45	156	81	
Percentage prescribed antibiotic/Indicator a	***38***	19	8		***67***	***48***	***69***		***78***	***57***	***86***		***62***	***45***	***75***		***80***	***54***	***33***		***69***	***67***	***77***		87	***67***	84	
Acceptable range (%)		0–20				0–20				0–20				0–20				0–30				90–100				80–100		
Percentage recommended antibiotic/Indicator b	***1***	***7***	***57***		***37***	***22***	***77***		***14***	***72***	87		***61***	81	91		***39***	83	***71***		***30***	***74***	***47***		***62***	83	***41***	
Acceptable range (%)		80–100				80–100				80–100				80–100				80–100				80–100				80–100		
b (percentage according to national guidelines)[c]	1	77	92		34	81	70		9	72	87		61	81	84		34	83	70		–	73	42		22	73	87	
Percentage quinolones/Indicator c	5	0.6	1		***11***	0.4	0		0	0.1	0		2	0.2	0		***15***	0.4	2		***19***	1.6	1		***22***	***7.4***	3	
Acceptable range (%)		0–5				0–5				0–5				0–5				0–5				0–5				0–5		
Antibiotic prescription per 1000 PY[d]	72	14	5		15	17	11		16	8	24		11	10	11		34	9	7		2	7	12		39	105	68	

[a]See Supplement 1 for ICPC-2-R and ICD-10 codes included in study.
[b]No. of consultations per 1000 registered patients.
[c]Percentage treated with first-choice antibiotic according to national guidelines (value not available for pneumonia in BE due to patients being sent to hospital for treatment).
[d]PY = No. of patient registered per year.
Values in italic and bold are outside the proposed acceptable range (see Table 1).

In Sweden, more than 70% of the patients consulting with sinusitis, tonsillitis or otitis media were prescribed an antibiotic (Indicator a). (Table 3) On the other hand, Sweden had the smallest proportion of antibiotic prescriptions for bronchitis (33%) and URTIs (8%). Less than half of the patients receiving antibiotics for pneumonia and cystitis were prescribed the APQI-recommended antibiotics (Indicator b). None of the indications exceeded the 5% upper limit of acceptable quinolone prescribing (Indicator c).

Comparison of number of prescriptions per 1000 PY

By combining consultation incidence and prescribing percentage, the numbers of prescriptions for the individual diagnoses can be calculated per 1000 PY, which is also presented in Table 3. Belgium had the highest number of prescriptions per 1000 PY for URTIs and bronchitis, the Netherlands for sinusitis and cystitis, and Sweden for tonsillitis and pneumonia. For otitis media this number was roughly similar for all three countries. For all RTIs including AOM, the Netherlands, Sweden and Belgium had 73, 80 and 150 prescriptions per 1000 PY, respectively. This difference is probably even larger given the higher percentage of prescriptions without a linked diagnosis in Belgium. For cystitis the number of prescriptions per 1000 PY were 105, 68 and 39, respectively.

Discussion

Main findings

We found that it was feasible to calculate the APQIs from routine data originating from EPR. For bronchitis and URTIs, the consultation incidence in Belgium was twice that of Sweden and the Netherlands. In Sweden, it was more common to consult for tonsillitis, and in the Netherlands for sinusitis and cystitis. GPs in the Netherlands and Sweden prescribed fewer antibiotics for RTIs than those in Belgium. We also noted that diagnoses with high consultation incidences resulted in high antibiotic prescribing measured per 1000 PY.

The results of the APQIs deviated from the proposed European ranges of acceptable values in 16, 10 and 9 out of the 20 indicators in Belgium, the Netherlands and Sweden respectively (Table 3).

Percentage of patients prescribed an antibiotic (Indicator a)

Results of this quality indicator showed that values deviated from the proposed acceptable ranges in all countries for sinusitis, tonsillitis, otitis media and

bronchitis. Only for URTIs in the Netherlands and Sweden were they within the proposed range, and for cystitis in Belgium and Sweden. Since the consultation incidences for each of the seven studied diagnoses varied substantially between the countries, the percentage of patients treated with an antibiotic (Indicator a) is not a valid instrument to compare prescribing quality between countries. A high consultation incidence but low prescribing percentage could result in the same number of prescriptions per 1000 PY as a low consultation incidence with a high prescribing percentage. Therefore, a better appreciation of the rate of antibiotic prescribing would be the number of prescriptions per given diagnosis, per 1000 registered patient [16].

The consultation incidence is influenced by several factors such as health care organisation, physician availability, public knowledge, requirements for sick notes, patient fee to consult a GP, as well as cultural differences [17]. In Sweden and the Netherlands, all patients call the general practice where a nurse will decide whether the patient needs an appointment with a physician, or can simply be advised on self-treatment, which might explain the relatively low number of consultations in those two countries. Consultation incidences could also be influenced by consultation fees per consultation (Belgium and Sweden) and the need for sickness certification within the first week of sick-leave (Belgium). The public knowledge about correct antibiotic use and antimicrobial resistance is slightly higher in Sweden than the other countries, which might decrease patients' demands for antibiotic treatment [18]. Illness perception and disease labelling differs, so that an episode of URTI in Belgium was referred to as bronchitis by the patients and antibiotics was used more often, while in the Netherlands it was called common cold [19].

Belgium is known to be a higher prescribing country with 2.53 packages per 1000 inhabitants per day (PID) compared to the Netherlands (1.53 PID) and Sweden (1.19 PID). We present PID values from 2009 as those are the most recent figures available for comparison between the three countries [20] (Table 2). This large difference in antibiotic prescribing between the countries was not identified in our data. Notably, however, 40% of the antibiotic prescriptions were not linked to a diagnosis in the Belgian data, and hence not part of our analysis, which might explain the less pronounced differences in our study. However, we clearly found more deviance from the proposed quality targets in Belgium, except for cystitis. The cystitis incidence was very low in Belgium compared to the other countries. The highest prescribing percentages in Belgian data were seen for bronchitis and URTIs, and since the consultation incidences for these two diagnoses were high as well, significantly higher numbers of prescriptions per 1000 PY were found as compared to the other countries. Hence, bronchitis and URTIs could be areas for further attention and possible intervention in order to improve antibiotic use in Belgium.

In the Netherlands, the prescribing percentages were higher than recommended for bronchitis, tonsillitis, sinusitis and AOM, and lower than recommended for cystitis. However, since the consultation incidences were low for all these diagnoses except for sinusitis, the numbers of prescription per 1000 PY were low. The fact that multiple consultations (within a 2 week period) for the same ICPC code account for only one episode in the Netherlands could have affected these figures, i.e. producing lower consultation incidences, and higher prescribing percentages when measured per episode instead of by consultation. Counting in episodes, however, does not affect the number of prescriptions per 1000 PY per diagnosis. The high use of antibiotics for cystitis has been noted earlier and the authors suggest further studies regarding adequate pain medication, enhanced diagnostic procedures and delayed prescribing [21].

Swedish figures showed higher prescribing percentages for AOM, sinusitis and tonsillitis compared to the other countries. Due to low consultation incidences, however, the prescription per 1000 PY was the same as in the other countries for AOM and actually lower than the other countries for sinusitis. For tonsillitis, the prescribing per 1000 PY was three times higher than in the Netherlands. The frequent use of rapid tests for Group A streptococci for sore throat in Sweden has been questioned and might have influenced consultation behaviour, and therefore tonsillitis has been identified as a target to improve antibiotic prescribing in Sweden [22,23]. Consequently, in late 2012, the national guidelines were revised in order to improve the selection of patients given antibiotic treatment [24]. Analysis of GPs' adherences to guidelines has been made in order to understand the reasons why the prescribing rate is high for tonsillitis in Sweden [25,26].

Percentage of patients receiving the recommended antibiotic (Indicator b + c)

Sixteen of the APQI values for percentage recommended antibiotics (Indicator b values for seven diagnoses for three countries) deviated from the proposed acceptable ranges. The outcome of this quality indicator was clearly influenced by differences in

recommendations between the national guidelines and the European consensus the APQI are based on. This was the case for sinusitis in the Netherlands (doxycyclin and amoxicillin are recommended) and in Sweden for cystitis (mecillinam and furantoin are recommended) and sinusitis and pneumonia (penicillin V is recommended) [27,28]. Using the antibiotics recommended by the national guidelines affected the results of indicator b significantly, which suggests that the antibiotic treatment advised by the national guidelines needs to be considered when interpreting APQI Indicator b.

The results of Indicator c were mainly of concern for Belgium, as the quinolone prescribing percentage exceeded the proposed 5% for four out of the seven diagnoses. Quinolone consumption is important to monitor, as it is a strong driver of bacterial resistance [29].

Reducing prescribing for URTIs and bronchitis in Belgium as well as decreasing the use of broad-spectrum antibiotics including quinolones would be the suggested strategy to improve antibiotic use according to the results of the APQIs.

Limitations of the study

We analysed data from routine daily primary care during office hours and out-of-hours consultations were not included, which could underestimate the antibiotic prescribing. The data used for comparison in this study were based on different databases and there may be inter-country variations in the recording of diagnoses and the efficiency and completeness of data recording. The extent of missing consultations cannot be evaluated, but the number of prescriptions not linked to a diagnosis, 40% for Belgium, 16% for the Netherlands and 26% for Sweden, shows that data are incomplete. Analysis of Swedish data showed that cystitis-related antibiotics were over-represented in the prescriptions not linked to a diagnosis, and including these would have increased the cystitis consultation incidence to approximate that of the Netherlands. Especially for cystitis, where patients do not need to see a GP, there may be differences in whether and how a prescription after a telephone consultation, or after history taking and a diagnostic test performed by the practice assistant/nurse, is registered with a diagnosis in the database. This could underestimate the consultation incidence and the prescribing for cystitis. Another explanation for the seemingly low consultation incidence and antibiotic prescribing for cystitis in Belgium is that the standard packages for nitrofurantoin contain tablets for treating three to four episodes, so the patient can self-treat new episodes without contacting the general practice. In the context of national data as well, we believe that our data have acceptable validity for evaluating prescribing quality for RTIs, but have limitations regarding cystitis.

Delayed prescribing could cause overestimation of the consumption of antibiotics if there were many prescriptions not collected by the patients. However, we believe that the strategy of delayed prescribing is used only to a limited extent, as it is not actively promoted in these countries [30]. Nevertheless, we should keep in mind that prescribing does not equal consumption, as was clearly shown for antibiotics prescribed for lower RTI by Francis et al. [31], and especially true in high prescribing settings.

Studies have shown that physicians' adherence to diagnostic coding systems is low due to the lack of clinically important diagnoses in the systems [32]. In situations where a diagnosis is better registered for treated patients than for untreated, there is a risk of overestimating the provision of treatment, which could be applicable for infectious diagnoses [33]. There could be differences between countries regarding physicians who use diagnosis to justify prescribing decisions, such as labelling bronchitis as pneumonia, which would underestimate the antibiotic prescribing for bronchitis. We must also be aware of possible case mix differences between the populations and that these can affect our data [34]. However, we believe the impact will be limited. In a recent European observational study on the management of lower RTI, controlling for case mix was not able to explain the huge variation in antibiotic prescribing [35].

Previous studies attempting to develop useful quality indicators have had difficulties in finding consensus and international validity [36–38]. For the APQI developed by ESAC and based on European consensus, we have shown that it is feasible to calculate values from primary care databases from more than one country [8,13]. Our findings, reflecting differences in practice between countries, will hopefully stimulate further national work on quality improvement. Ultimately, the concurrent validity of quality indicators should be tested against a gold standard [39,40].

Conclusion and further direction

APQIs are developed to assess the quality of antibiotic prescribing in primary care using diagnosis-linked prescription data, and to allow comparison between European countries. The APQIs could provide direction for improvement strategies such as public campaigns, physician education or organisational changes in healthcare. However, completeness of data,

incorporation of consultation incidence and the nationally recommended antibiotics, knowledge of each country's specific organisation and praxis, especially for cystitis, are essential for proper interpretation of APQI values. Then APQIs could represent a useful tool to evaluate and compare prescribing quality in primary care antibiotic internationally.

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Supplement 1: List of corresponding diagnostic coding between ICPC-2-R and ICD-10.

ICPC-2-R	ICD-10
H71	H66.0, H66.4, H66.9, H67.0, H67.1, H67.8, H70.0, H73.0
R74	B00.2, B08.5, J00, J02.8, J02.9, J06.0, J06.8, J06.9
R75	J01.0-J01.9, J32.0-J32.9
R76	J03.8, J03.9, J36
R78	J20.0-J20.9; J21.0, J21.8,J21.9, J22, J40
R81	A48.1, J10.0, J11.0, J12.0-J12.9, J13, J14, J15.0-J15.9, J16.0, J16.8, J17.0-J17.8, J18.0-J18.9
U71	N30.0-N30.9, N39.0

Paper III

Tyrstrup *et al. BMC Infectious Diseases* (2017) 17:603
DOI 10.1186/s12879-017-2703-3

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Children with respiratory tract infections in Swedish primary care; prevalence of antibiotic resistance in common respiratory tract pathogens and relation to antibiotic consumption

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Abstract

Background: The majority of antibiotics consumed in developed countries are prescribed in primary care. However, little is known about resistance levels in the primary care population.

Method: Nasopharyngeal cultures were obtained from children, 0-10 years of age, seeking care at their Primary Health Care Centre with symptoms of respiratory tract infection. Parental questionnaires were used to retrieve information about the child's previous antibiotic consumption.

Result: Cultures from 340 children were gathered. The level of resistant *Haemophilus influenzae* was low and the prevalence of penicillin non-susceptible pneumococci (PNSP MIC ≥ 0.125 mg/L) was 6% compared to 10% ($p = 0.31$) in corresponding cultures from children diagnosed at the local clinical microbiology laboratory. Antibiotic treatment within the previous 4 weeks predisposed for resistant bacteria in the nasopharynx, OR: 3.08, CI 95% (1.13-8.42).

Conclusion: Low prevalence of PNSP supports the use of phenoxymethylpenicillin as empirical treatment for childhood upper respiratory tract infections attending primary care in our setting. It is important that studies on resistance are performed in primary care populations to evaluate data from microbiological laboratories. Recent antibiotic treatment increases risk of bacterial resistance in children and continuous work to reduce unnecessary antibiotic prescribing should be prioritised.

Background

In Swedish Primary Health Care (PHC) about one-third of all consultations are regarding infections, of which some 60% concern respiratory tract infections (RTIs), such as acute otitis media (AOM), sinusitis and pneumonia [1]. A common pathogen causing these conditions in children is *Streptococcus pneumoniae* [2, 3]. *S. pneumoniae* can also cause severe invasive disease, especially in young children and the elderly. In Sweden about 2-3 children under the age of five die due to invasive pneumococcal disease each year. Since the pneumococcal vaccine was introduced in Sweden in 2009 the incidence of serious pneumococcal infections in children under the age of two has been reduced by 70% [4]. In healthy children attending daycare in Sweden, the prevalence of *S. pneumoniae* in the nasopharynx (NP) is about 60% [5] and the prevalence decreases with age from the second year of life [6, 7] to about 5% in an adult population [8]. Phenoxymethylpenicillin (Penicillin V) is the drug of choice for empirical treatment of respiratory tract infections in Scandinavia and is recommended in the national guidelines. In therapeutic failure or if an appropriate culture shows growth of penicillin non-susceptible pneumococci (PNSP, MIC ≥ 0.125 mg/L) or *Haemophilus influenzae* second-line treatment with amoxicillin is advised.

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The vaccination program in Sweden includes *Haemophilus influenzae* type B- and the 13- valent pneumococcal vaccine. The current coverage for at least three doses of these vaccinations in Sweden is 97%, calculated on all children registered with a Primary Health Care Centre (PHCC), which include 99% of all 2-year old children registered in Sweden in 2016 [4].

In 1967 the first report of a strain of penicillin non-susceptible *S. pneumoniae* (PNSP MIC ≥ 0.125 mg/L), was encountered in Australia [9] and in the following decade reports of PNSP followed from many other countries. High frequencies of PNSP, around 20% in invasive isolates were noted in central and southern parts of Europe, such as in France, Spain and Hungary in 2011 and in Germany, the Netherlands and the Nordic countries frequencies below 5% have been reported [10]. Iceland had an increase of PNSP at the beginning of the 1990s in hospital isolates to a level of 20% in 1993 [11], while the level in PHC was about 10% during the same year [12]. The frequency of PNSP has been found to correlate to antibiotic prescription at an individual as well as at community level [11–14].

In the early 1990s, an increase of PNSP (MIC ≥ 0.125 mg/L) from 3 to 11% was also noted in Sweden [15]. An epidemic spread of several clones of PNSP was seen in the southernmost part of Sweden and the South Swedish Pneumococcal Intervention Project was launched to curb the spread [16]. Since then, a low prevalence of PNSP (4%) has been noted in surveys of healthy toddlers in Sweden [17], but there has been an increase in incidence from 3.7% in 1994 to 9.8% in 2015 in the data reported from the microbiological laboratories (ResNet) [18].

Haemophilus influenzae is the second potential pathogen targeted when treating RTIs with antibiotics, causing epiglottitis and invasive disease including pneumonia. However, since the vaccination against *H.influenzae* type b (Hib) was introduced into developed countries these severe conditions have decreased substantially, though they are still present in developing countries where vaccination coverage is low [19]. *H.influenzae* colonises the NP of up to 50% of healthy children [20] and are responsible for about one-third of all episodes of AOM in children [21].

The first report of beta-lactamase producing *H.influenzae* came in 1974 [22]. Penicillin resistance in *H.influenzae* is most often conferred by production of beta-lactamase, or by chromosomally mediated mechanisms, called beta-lactamase negative ampicillin resistant *H.influenzae* (BLNAR). Some *H.influenzae* strains have both of these resistance mechanisms. Since 2013, beta-lactamase producing *H.influenzae* has shown a decreasing trend, with a prevalence of around 16% in 2015 and BLNAR, with an increasing trend and a prevalence of 19% in 2015 in Sweden [18]. The trends are similar in other countries [23]. Around the world, the prevalence of beta-lactamase producing *H.influenzae* varied between 5 and 39% in 2003 [24] and the prevalence of BLNAR around 10% in Europe in 2000, but up to 40% in Japan [23] in data from microbiological laboratories.

National data on antibiotic resistance in Sweden are based on cultures from NP swabs from both hospital and primary care patients. The 25 microbiological laboratories each annually report ≥100 consecutive strains per pathogen to the national register Res-Net (Swedres/ SWARM 2016, p.110-111, www.folkhalsomyndigheten.se). In PHC it is only recommended to perform swabs on patients with AOM when first-line treatment has failed or in recurrent infections, and not in children seeking primary care with their initial symptoms of RTI. The true level of bacterial resistance in children with RTI symptoms consulting PHC remains unknown and the results from the laboratory may therefore not be valid in a PHC setting.

The aim of this study was to evaluate the prevalence of PNSP and beta-lactamase producing *H.influenzae* and BLNAR in children with symptoms of RTI presenting at Primary Health Care Centres (PHCCs) and to compare our findings with those of routine microbiological lab data.

Furthermore, we wanted to investigate the relation between presence of resistant bacteria (PNSP, beta-lactamase producing *H.influenzae*, BLNAR) and previous antibiotic consumption and other risk factors.

Methods

We performed a cross-sectional study on children, 0-10 years of age, registered at 12 different PHCCs in the county of Scania, in the southernmost part of Sweden. The sizes of the PHCCs varied from two up to 15 serving physicians. The PHCCs were chosen to represent both urban (four PHCCs) and rural (eight PHCCs) areas of the region, including the city of Malmo with approximately 320.000 inhabitants. The antibiotic prescription rates of the PHCCs were similar to the average prescription rate of the county. In 2013 the county of Scania had a population of 1.274.069 inhabitants, of which 167.484 were children aged 0-10 years [25]. Aiming to collect 100 pneumococcal isolates, and based on 2013-2014 regional microbiological laboratory data with the carriage rate of 30% in 0-10 year olds (E. Melander, personal communication, May 30, 2016) we estimated a need for approximately 400 NP specimens.

Data collection

Children, aged 0-10 years, consulting their PHCC with symptoms of RTI, between 1st Nov 2013 until 30th April 2014 and 1st Nov 2014 until 30th April 2015 were

included. Information about the study and a written invitation was given to the parents at arrival at the clinic and informed parental consent was obtained for each case. Lack of knowledge of the Swedish language was the only exclusion criterion.

Questionnaires

The parents were asked to fill out a questionnaire regarding factors believed to affect bacterial resistance, such as the child's age, antibiotic consumption over the last year and specifically during the last 4 weeks, type of day care, number of siblings, travel abroad, hospital admissions etc. (Additional files 1 and 2). The same patient was only included once. The individual antibiotic consumption was evaluated via the questionnaire filled out by the parents.

Sample collection and bacterial analysis

NP specimens were obtained in a standardised manner by trained laboratory personnel at the PHCCs. A swab (ESwab ™ Liquid Amies Collection and Transport System, COPAN) [26] was taken from the rear wall of the nasopharynx, where the stick was kept still for 10 s before being withdrawn. The test swab was kept in a refrigerator until being sent to the Department of Clinical Microbiology in Malmö/Lund where it was analysed for *S.pneumoniae*, *H.influenzae*, *Moraxella catarrhalis* and beta-haemolytic streptococci group A, according to national recommendations [27]. Antibiotic susceptibility testing was performed according to recommendations of the EUCAST [28]. Isolated *S.pneumoniae* were screened for penicillin resistance by disc diffusion test using 1-microgram oxacillin discs. Minimum inhibitory concentration (MIC) for benzylpenicillin was determined by E-test in isolates with inhibition zones <20 mm. *S.pneumoniae* with MIC of ≥0.125 mg/L was considered penicillin non-susceptible (PNSP). Screening for beta-lactam resistance in *H.influenzae* was performed by disk diffusion test using benzylpenicillin discs. If found to be benzylpenicillin resistant, a beta-lactamase test was performed (Nitrocefin). For detection of chromosomal penicillin resistance (BLNAR), a disk diffusion test was used with a beta-lactamase stable cephalosporin (cefaclor) as an indicator.

In this paper, colonization with resistant bacteria was defined as the presence of PNSP and/or *H.influenzae* strains with beta-lactamase production and/or *H.influenzae* with chromosomal resistance, (BLNAR).

Statistical analysis

The main outcome was the presence of PNSP and resistant *H.influenzae* in the NP culture. Questionnaire and laboratory data were collected in Microsoft Excel and statistical analysis was performed using SPSS 22.0 software (IBM, Armonk, NY, USA). Descriptive statistics are presented as numbers and proportions. Comparisons between proportions for categorical variables in two independent groups were performed using the two-sided χ^2-test. Multiple logistic regressions were used to model the relationship between the outcome variable (carriage of resistant bacteria) and several independent variables (risk factors for carriage of resistant bacteria retrieved from the parental questionnaire).

Results

Baseline data

Of the 12 PHCCs, eight provided 90% of the NP cultures. We aimed at collecting 400 cultures but managed 340 due to declining recruitment. Altogether, 422 children were recruited, of which 340 participated with NP cultures and the parental questionnaire. A total of 82 children did not accept having nasopharyngeal culture taken (Fig. 1). The baseline characteristics of the children with and without a nasopharyngeal culture taken were similar (Table 1). The median age in both groups was 2.0 years (IQR = 1-5).

Of the 340 children, 86 (25%) carried *S.pneumoniae*, 129 (38%) *H.influenzae*, 185 (54%) *M.catarrhalis*, 24 (7%) beta haemolytic streptococci group A and 69 (20%) were culture negative or carried non-target organisms (Table 2). Of the 86 isolates with *S.pneumoniae,* five (6%) were PNSP all with MIC = 0.125 mg/L. Three of these PNSP isolates also showed resistance to trimethoprim, one showed additional resistance to tetracycline and one additional resistance to tetracycline, erythromycin and clindamycin. Resistance data are presented in Table 2.

Factors associated with bacterial resistance

When analysing the 340 children from which NP cultures were taken, we found that having received antibiotic treatment (predominately Penicillin V) within the previous 4 weeks predisposed for resistant bacteria (OR = 3.08, 95% CI (1.13-8.42). Antibiotic consumption during the last year did not significantly affect the prevalence of resistant bacteria in our analysis. But, since it could interact with the variable antibiotic consumption the previous 4 weeks we decided to exclude it in the regression analysis. The risk of carrying resistant bacteria also decreased with age (OR = 0.75, 95% CI (0.57-0.99) (Table 3).

In 178 (52%) of the cultures, there was growth of either *S.pneumoniae* or *H.influenzae* or both, of which 40 (22%) isolates showed some sort of resistance to beta-lactam antibiotics, either PNSP, and/or beta-lactamase producing *H.influenzae* and/or BLNAR (Fig. 1).

When analysing only the 178 children with growth of either *S. pneumoniae* or *H. influenzae,* or both, we noted that boys were more commonly colonised with resistant

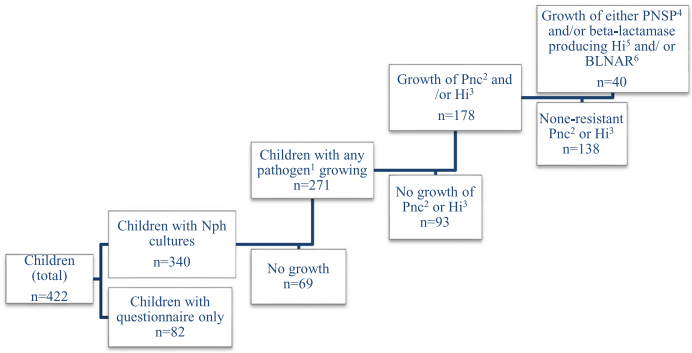

Fig. 1 Flow chart of children in the study. [1] Either *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* or Group A Streptococci. [2] *Streptococcus pneumoniae*. [3] *Haemophilus influenzae*. [4] penicillin non-susceptible *Streptococcus pneumoniae*. [5] beta-lactamase producing *Haemophilus influenzae*. [6] beta-lactamase negative ampicillin resistant *Haemophilus influenzae*

Table 1 Demographic and clinical data of study population

Variable	Number (%)			
	All children with Nph[a] culture (*n* = 340)	Children with growth of either Pnc[b] and/ or Hi[c] (*n* = 178)	Children with growth of either PNSP[d] and/ or beta-lactamase producing Hi[e] and/ or BLNAR[f] (*n* = 40)	Questionnaire only (*n* = 82)
Female	162 (48)	92 (52)	14 (35)	41 (50)
Age (0-5 years)	275 (81)	160 (90)	38 (95)	65 (79)
Hospital care last 6 months	11 (3)	7 (4)	2 (5)	1 (1)
Abroad last 3 months	81 (24)	43 (24)	10 (25)	21 (26)
Parents smoking	43 (13)	16 (9)	2 (5)	10 (12)
Day care:				
Attending day care centre	224 (67)	137 (77)	33 (83)	56 (68)
Attending school	60 (18)	7 (4)	1 (3)	16 (20)
Home	52 (15)	24 (14)	6 (15)	9 (11)
Respiratory tract disease (asthma/ allergy)	34 (10)	20 (11)	1 (3)	9 (11)
Pneumococcal vaccination:				
Don't know	94 (28)	40 (22)	9 (23)	30 (37)
Yes	218 (64)	128 (72)	28 (70)	46 (56)
No	28 (8)	10 (6)	3 (8)	6 (7)
Number of antibiotic treatments during last 12 months:				
> 3	22 (6)	11 (6)	4 (10)	6 (7)
1-2	98 (29)	46 (26)	12 (30)	19 (23)
None	182 (54)	105 (59)	21 (53)	57 (70)
Antibiotic treatment within the last 4 weeks	32 (9)	15 (8)	7 (18)	5 (6)

Missing data were 20% regarding "Number of antibiotic treatments during last 12 months", similar in all groups. In the other variables missing data were <10% in all groups
[a]Nasopharyngeal culture
[b]*Streptococcus pneumoniae*
[c]*Haemophilus influenzae*
[d]penicillin non-susceptible *Streptocuccus pneumoniae*
[e]beta-lactamase producing *Haemophilus influenzae*
[f]beta-lactamase negative ampicillin resistant *Haemophilus influenzae*

Table 2 Data on isolated bacteria in nasopharyngeal cultures of children 0-10 years during November 2013-April 2014 and November 2014-April 2015, in the study and in routine laboratory data

	Our data (primary care)	Routine laboratory data (primary care and hospital care)
Number of cultures	340	1854
Streptococcus pneumoniae	86 (25%)	468 (25%)
PNSP[a] (MIC ≥ 0.125 mg/L)	5 (6%) All with MIC = 0.125 mg/L	47 (10%) Of which: 32 MIC = 0.125 mg/L 6 MIC = 0.25 mg/L 4 MIC = 0.5 mg/L 4 MIC = 1 mg/l 1 MIC = 2 mg/L
Erythromycin resistant	4 (5%)	32 (7%)
Clindamycin resistant	3 (3%)	25 (5%)
Tetracycline resistant	4 (5%)	23 (5%)
Trimethoprim resistant	7 (8%)	53 (11%)
Haemophilus influenzae	129 (38%)	747 (40%)
Beta-lactamase producing	21 (16%)	96 (13%)
BLNAR[b]	16 (12%)	57 (8%)
Moraxella catarrhalis	185 (54%)	1524 (82%)
Group A streptococci	24 (7%)	138 (7%)

[a]penicillin non-susceptible pneumococci
[b]Beta-lactamase negative ampicillin resistant *Haemophilus influenzae*

bacteria (OR = 2.95, 95% CI (1.25-6.98) (Table 4). No significant association was found between resistance and hospital care, travelling abroad, parental smoking, day care attendance, respiratory tract disease (asthma/allergy) or pneumococcal vaccination (Tables 3 and 4).

Comparison with data from the local clinical microbiology laboratory

The prevalence of *S.pneumoniae* and *H.influenzae* were similar to the data from the local clinical microbiology laboratory for the same period and age group (Table 2). We could not identify any statistically significant difference in the prevalence of PNSP (p = 0.31), beta-lactamase producing *H.influenzae* (p = 0.33) or BLNAR (p = 0.08) between our community study and the data from the local clinical microbiology laboratory (Table 2).

Discussion

Main findings

We found a low prevalence of PNSP and resistant *H.influenzae* among respiratory tract pathogens in children with symptoms of RTIs in primary care, indicating that phenoxymethylpenicillin is valid as empirical treatment for these patients, if antibiotics are required. We noted no

Table 3 Risk factors for carriage of resistant bacteria* among children aged 0-10 years with respiratory tract symptoms in Primary Health Care. (n = 340)

Variable	Crude OR (95% CI)	Adjusted **OR (95% CI)
Male sex	1.81 (0.91-3.60)	
Age (per year)	0.81 (0.69-0.95)	0.75 (0.57-0.99)
Hospital care last 6 m	1.70 (0.35-8.14)	
Abroad last 3 m	1.08 (0.50-2.31)	
Parents smoking	0.33 (0.08-1.43)	
Attending day care centre	2.69 (1.15-6.29)	2.63 (0.91-7.66)
Respiratory tract disease (asthma/ allergy)	0.20 (0.03-1.47)	
Pneumococcal vaccination (yes)	1.23 (0.35-4.34)	
Antibiotics previous 4 weeks	2.33 (0.94-5.81)	3.08 (1.13-8.42)

Missing data regarding the variables were <10% in the children with, as well as, in the children without resistant bacteria
*Growth of either penicillin non-susceptible pneumococci (PNSP) and/ or beta-lactamase producing *Haemophilus influenzae* and/or beta-lactamase negative ampicillin resistant *Haemophilus influenzae* (BLNAR)
**Method: Backward Stepwise (Wald) Step 7

Table 4 Risk factors for carriage of resistant bacteria among children aged 0-10 years with respiratory tract symptoms in Primary Health Care and growth of either *Streptococcus pneumoniae* and/or *Haemophilus influenzae*. (n = 178)

Variable	Crude OR (95% CI)	Adjusted *OR (95% CI)
Male sex	2.41 (1.16-5.02)	2.95 (1.25-6.98)
Age (per year)	0.85 (0.70-1.04)	0.77 (0.58-1.02)
Hospital care last 6 m	1.40 (0.26-7.50)	
Abroad last 3 m	1.06 (0.47-2.40)	
Parents smoking	0.47 (0.10-2.14)	
Attending day care centre	1.54 (0.63-3.80)	
Respiratory tract disease (asthma/ allergy)	0.17 (0.02-1.28)	0.17 (0.02-1.38)
Pneumococcal vaccination (yes)	0.65 (0.16-2.69)	
Antibiotics previous 4 weeks	3.45 (1.17-10.19)	

Missing data regarding the variables were <10% in the children with, as well as, in the children without resistant bacteria
*Method: Backward Stepwise (Wald) Step 7

significant differences in prevalence of PNSP and resistant *H. influenzae* in our results compared to the local microbiological laboratory. Studies based on primary care populations are important for validation of resistance measures from microbiological laboratory findings due to differences in case-mix. Treatment with antibiotics, within the previous 4 weeks predisposed for resistant bacteria supporting continued efforts to rationalise antibiotic use.

Strengths and weaknesses

Previous attempts to investigate bacterial resistance in RTIs in primary care have studied populations containing a mix of children attending PHCCs as well as those seeking care at hospital emergency rooms [29, 30]. The strength of this study is that the population consists of primary care patients only. Bearing in mind that most antibiotics are prescribed in primary care, monitoring resistance levels in this population should be of importance to appreciate the true burden of resistance as well as for the development of guidelines and recommendation of empirical antibiotic choice. Based on the carriage rate of *S.pneumoniae* in Swedish children we estimated a need of 400 cultures to identify about 100 isolates of *S.pneumoniae*, but we settled with 340 cultures and 86 isolates due to a declining recruitment rate. We chose to recruit during the winter season because the consultations for RTIs are more common at that time of the year. We do not believe that the few cases missed during the rest of the year would affect our result. We deem the risk of patient selection bias to be low because although we received a variable number of cultures from the different PHCCs, indicating difficulties in recruiting patients, we noted that most parents were willing to participate in the study once they were asked. Furthermore, the only exclusion criterion was lack of knowledge of the Swedish language. Ongoing treatment with antibiotics was not asked about, and therefore not an exclusion criterion. We had a good response rate regarding antibiotic use the previous 4 weeks, which to most parents include whether the child are on any current antibiotic treatment. The use of routine sample collection and well-established methods for analysis of NP cultures should ensure the reliability of the results.

The number of antibiotic prescriptions during the last year was difficult for some parents to answer for in the questionnaire and therefore we saw around 20% missing data regarding this question. However, since the missing data were equally distributed in the groups, with and without resistance, it should not affect the regression analysis.

The association between antibiotic consumption during the previous 4 weeks and bacterial resistance showed an OR with a wide 95% confidence interval due to a small number of children that had taken antibiotics within the 4 weeks prior to the culture and a small number with beta-lactam resistant strains. Although there is some insecurity in the result due to the small sample size it should be possible to infer to similar populations.

To differentiate whether our results represent colonisation or infection is not possible. The fact that the children all presented with symptoms of RTIs, such as fever, cough, sore throat, earache or runny nose supports the theory of it representing an infection, but, the culture might not represent the etiological agent. We did not perform any respiratory virus testing, which could explain some of the symptoms. Treatment information and outcome data could also have helped in the differentiation between colonisation and infection, although most RTIs, whether caused by bacteria or virus are self-healing. Since serotyping of the pneumococci was not performed we don't know if they were covered in the 13-valent vaccine used in Sweden.

Previous studies

We found that 25% of the children seeking care at their PHCC for RTI symptoms and who were recruited to our

study carried *S.pneumoniae* and 38% carried *H.influenzae.* These figures were in line with other recent European and American studies [7, 29, 31, 32].

By contrast, the level of PNSP (MIC ≥ 0.125 mg/L) was lower in our study than in many other countries [24, 32, 33]. PNSP levels are known to be correlated to antibiotic consumption [6]. Over the last 20 years, great reductions in antibiotic prescribing for RTIs in Swedish PHC have been achieved [34], which is likely to have played an important role in the reduction of PNSP over time. Swedish guidelines for RTIs recommend phenoxymethylpenicillin as first line treatment to target the pneumococci, and the low level of resistance found in this study supports that recommendation. By contrast, the prevalence of beta-lactamase producing *H.influenzae* does not seem equally influenced by the reduced levels of antibiotics. The beta-lactamase producing *H.influenzae* has remained between 15 and 18% in Sweden since 2007 and we see a continuous increase in BLNAR [18]. Previously, we have seen a similar development for *Moraxella catarrhalis,* of which now 95-98% is beta-lactamase producing in every setting [24, 33].

Antibiotics have been shown to affect our bacterial flora so that penicillin sensitive pneumococci decreases 1 month after antibiotic therapy [7] as does penicillin sensitive *H.influenzae* [35]. Moreover, antibiotic use is associated with increased prevalence of PNSP [12, 36–38] and BLNAR [39], but only some studies show antibiotic consumption to be a risk factor for carrying beta-lactamase producing *H.influenzae* [40–42] while others do not [31, 43, 44].

When we considered only the children with growth of either *S.pneumoniae* or *H.influenzae* (n = 178) we found that boys were more often colonised with resistant bacteria than girls, which is supported by some previous studies [36] but not by others [12]. Boys have also been shown to catch more RTIs in younger ages than girls [45, 46] and develop complications to AOM more often [47]. The reasons for these differences between the sexes are not known.

Other risk factors for carrying PNSP (MIC ≥ 0.125 mg/L) have been reported in previous studies with various results. Some studies support our findings that younger age predisposes to PNSP carriage [12, 31, 36], and also longer duration of PNSP carriage [36] Other studies show that attending a day care centre increases the risk [31] while the number of siblings, presence of respiratory tract disease and parental smoking did not affect resistance levels in the studies mentioned above, nor in our results.

A lower PNSP prevalence in a PHC population compared to local microbiology laboratory data, as was seen in Iceland in 1993 [11, 12] may be due to patient selection. In the Swedish guidelines, it is only recommended to perform NP swabs on patients with RTIs when first-line treatment has failed or in recurrent infections. The local microbiology laboratory data also includes cultures from hospital patients, both admitted and attending Emergency services and in some cases also patients referred from primary care. The differences in case-mix provide support for regular measurements of resistance in primary care populations to validate laboratory resistance data. In many counties in Sweden there has also been a relative reduction in the number of performed NP swabs (Swedres/ SWARM 2001-2016, www.folkhalsomyndigheten.se) and the cultured isolates therefore may exaggerate the prevalence of resistance, which in turn could have implications for treatment guidelines and empirical choice of antibiotics.

The carriage rates of *H.influenzae* were similar in our findings and the local microbiological laboratory data, as were the levels of beta-lactamase *producing H.influenzae* and BLNAR.

Conclusion

The prevalence of resistant bacteria in the upper respiratory tract in young children in Swedish primary care was low. Phenoxymethylpenicillin can therefore still be recommended for empirical treatment. In order to provide a basis for empirical therapies resistance data from microbiological laboratories should be validated by regular studies on primary care populations. Our results support the fact that recent antibiotic treatment increases bacterial resistance in children and continuous work to reduce unnecessary antibiotic prescribing should be prioritised.

Additional files

Additional file 1: Parental questionnaire in English. (DOCX 25 kb)
Additional file 2: Parental questionnaire in Swedish. (DOCX 26 kb)

Abbreviations

AOM: Acute otitis media; BLNAR: Beta-lactamase negative ampicillin resistant; Hib: *Haemophilus Influenzae* type b; NP: Nasopharynx; Penicillin V: phenoxymethylpenicillin; PHC: Primary Health Care; PHCC: Primary Health Care Centre; PNSP: Penicillin non-susceptible pneumococci; RTI: Respiratory tract infection

Acknowledgements

We thank Dr. Ann-Cathrine Petersson and Lena Hyllebusk, Department of Microbiology at Lund University for help with coordinating culture methods and susceptibility testing. We are very grateful for the cooperational work performed by medical personnel at each of the participating PHCCs.

Funding

Southern Regional Health Care Committee, Sweden.

Availability of data and materials

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

Authors' contributions
SM and MT initiated the study. MT collected and registered the data. MT, AB and KH performed the calculations and statistical analysis. EM provided data from the local Microbiological laboratory. MT drafted the manuscript. All authors contributed in the analysis and commented on the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethical Review board at Lund University, (Dnr. 2013/ 513). Information about the study and a written invitation was given to the parents at arrival at the clinic and informed parental consent was obtained for each case.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Received: 5 June 2017 Accepted: 22 August 2017
Published online: 04 September 2017

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lab-etiquette

Today´s date:_____
Social security number of the child:

_ _ _ _ _ _ - _ _ _ _

Research study: Prevalence of resistant bacteria in children, age 0-10 years. Questionnaire to be completed by accompanying adult:

Age of child (years):_____ girl☐ boy☐

1. **Main activity of child during daytime:**

School☐ Preschool☐ At home☐ Don´t know☐

2. **Number of household members:**_____
Number of children 0-6 years of age, in your household:____

3. **Smokers in the family?** Yes☐ No☐ Don´t know☐

4. **Does the child have any previous illness in the airways, such as asthma, allergy or other?**

If yes, which illness:_____ No☐ Don´t know☐

5. **Is the child vaccinated against pneumococci?** Yes☐ No☐ Don´t know: ☐

6. **Has the child been admitted to hospital in the last 6 months?**

Yes☐ No☐ Don´t know: ☐

7. **Has the child travelled abroad in the last 3 months?** Yes☐ No☐ Don´t know: ☐

8. **How many treatments with antibiotics has the child received during the last year?**

0☐ 1-2☐ 3 or more☐ Don´t know: ☐

9. **Has the child been treated with antibiotics the last 4 weeks?**

Yes☐ **Name of antibiotic:**_____ No☐ Don´t know: ☐

10. **Which symptoms does the child present with today?**

cough☐ cold☐ sore throat☐ ear ache☐ fever☐

other☐ Don´t know☐

11. **Was the child prescribed antibiotics at today's visit?**

If yes, which antibiotic?_____ No☐ Don´t know☐

12. **Approval of researchers' access to medical register?** Yes☐ No☐

13. **Choose to participate with swab from the nose**. Yes☐ No☐

Thank you for your time!
Please, leave the questionnaire in the reception or lab.

Plats för labb-etikett

Dagens datum:_____

Barnets personnummer (10 siffror):

_ _ _ _ _ _ - _ _ _ _

Forskningsstudie för kartläggning av motståndskraftiga bakterier hos barn, 0-10 år. Frågor till vårdnadshavare/medföljande vuxen:

Barnets ålder (hela år):_____ Flicka☐ Pojke☐

1. **Var vistas barnet dagtid?**

   ☐Skola ☐Fritids ☐ Förskola ☐ Dagmamma ☐ Hemma enbart ☐Vet ej

2. **Hur många bor i ert hushåll?____**
   Hur många är barn 0-18 år?____

3. **Röker någon i familjen?** Ja☐ Nej☐ Vet ej☐

4. **Har barnet någon bakomliggande sjukdom i luftvägarna (tex astma, allergi eller annat)?**

   Ja, vad:_____ Nej☐ Vet ej☐

5. **Är barnet pneumokockvaccinerat? (ingår i basprogrammet på BVC sedan 2009)**

   Ja☐ Nej☐ Vet ej☐

6. **Har barnet varit inlagd på sjukhus de senaste 6 månaderna?** Ja Nej☐ Vet ej☐

7. **Har barnet varit utomlands de senaste 3 månaderna?** Ja ☐ Vilket land?_____ Nej☐ Vet ej☐

8. **Hur många kurer med antibiotika har barnet använt det senaste året:**

   0:____1-2:_____ >3:_____ Vet ej☐

9. **Har barnet fått antibiotika de senaste 4 veckorna?**

   Ja☐ Vilket preparat?_____ Nej☐ Vet ej☐

10. **Vilka besvär från luftvägarna gör att ni söker läkare idag?**

    Hosta☐ Snuva☐ Halsont☐ Ont i öronen☐ Feber☐ Annat: _____ Vet ej☐

11. **Förskrevs barnet antibiotika vid dagens läkarbesök?**

    Om, ja, vilket preparat?_____ Nej☐ Vet ej☐

12. **Medgivande att gå in i läkemedelsförteckningen (apotekets register för utskrivna läkemedel).**

    Ja☐ Nej☐

13. **Lämnar prov från näsan (nasopharynxodling) idag:** Ja ☐ Nej☐

Tack för besväret!

Vänligen lämna lappen till den som tar näsprovet (nasopharynxodlingen.)

Quality in antibiotic prescribing in primary care

A thesis comprised of four studies on different aspects of quality in antibiotic prescribing in Swedish primary care. Included are register studies on current practice and trends in antibiotic prescribing among Swedish General Practitioners, evaluation of European antibiotic prescribing quality indicators, analysis of antimicrobial resistance in common respiratory pathogens in children in primary care and qualitative aspects on national guidelines.

Mia Tyrstrup is a Specialist in General Medicine and has been working in Primary Health care since 2006. The thesis was completed during the years 2013-2017 at the Department of Clinical Sciences in Malmö, Lund University, Sweden.

World Antibiotic Awareness Week 2015: Campaign visual identity "Antibiotics: Handle with care". www.who.int

General Practice/ Family Medicine
Department of Clinical Sciences in Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2017:135
ISBN 978-91-7619-518-5
ISSN 1652-8220

LUND UNIVERSITY
Faculty of Medicine

Printed by Media-Tryck, Lund 2017 NORDIC ECOLABEL, 3041 0903