Treatment of Respiratory Tract Infections in Primary Care with special emphasis on Acute Otitis Media

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To Ann-Sofie, Sandra, Diana and Marcus

the truth's words

“...the warning against the indiscriminate use of the antibiotic is timely. Possibly Fleming might have further emphasized the dangers which may accrue from the promiscuous use of the product in conditions in which the causative organisms are not identified or in which other forms of treatment are known to be effective. Not only is this practice unsound but it may have the effect of reducing the efficacy of penicillin in patients confronted by a lethal emergency caused by pathogens which would have been susceptible under ordinary circumstances”

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ABSTRACT

Background and aims: Most respiratory tract infections (RTI) are self-limiting. Despite this, they are associated with high antibiotic prescription rates in general practice in Sweden. The aim of this thesis was to evaluate the management of respiratory tract infections (RTIs) with particular emphasis on acute otitis media (AOM).


Results: Children with AOM who received PcV had some less pain, used fewer analgesics and consulted less, but the PcV treatment did not affect the recovery time or complication rate (I). Between 1999 and 2005, 240 445 visits for RTI were analyzed (II & III). Antibiotics were prescribed in 45% of visits, mostly PcV (60%) and doxycycline (18%). Visiting rates for AOM and tonsillitis declined by >10%/year, but prescription rates of antibiotics remained unchanged. For sore throat, 65% received antibiotics. Patients tested but without presence of S.pyogenes received antibiotics in 40% of cases. CRP was analyzed in 36% of consultations for RTI. At CRP<50mg/l antibiotics, mostly doxycycline, were prescribed in 54% of visits for bronchitis. Roughly 50% of patients not tested received antibiotics over the years. Twelve of 71 children with AOM and spontaneous perforation completing the trial received antibiotics during the first nine days due to lack of improvement, one child after 16 days due to recurrent AOM and six had new incidents of AOM after 30 days (IV). Antibiotics were used more frequently when the eardrum appeared pulsating and secretion was purulent and abundant. All patients with presence of S.pyogenes received antibiotics.

Conclusions: The benefit of antibiotic treatment of uncomplicated AOM in children aged 2-16 was limited. The result support the “wait and see” approach in uncomplicated AOM.
Abstract

Consultations for RTI have decreased by 23% and the total number of antibiotic prescriptions by 33% between 1999 and 2005. Visits for AOM and sore throat decreased by over 10% per year, but visit-related prescription rates of antibiotics remained unchanged implying that the new guidelines may have influenced patient consultation habits more than physician prescribing habits. Near-patient tests were used extensively, and results were often used and interpreted not in accordance with the guidelines, resulting in improper antibiotic prescription.

Most children with AOM complicated with spontaneous perforation can be followed applying an active “wait and see” policy during the first 3 days of infection. Children with abundant purulent otorrhea and presence of \textit{S.pyogenes} in aural secretion could benefit by immediate antibiotics.

\textit{Keywords:} General practice, respiratory tract infections, acute otitis media, rapid diagnostic tests, CRP, Strep-A, electronic patient records, physician consultations, antibiotic prescription
LIST OF PAPERS

The thesis is based on four original investigations, presented in the following papers, which are referred to in the text by Roman numerals:

Evaluation of phenoxympenylpenicillin treatment of acute otitis media in children aged 2-16.

II. Neumark T, Brudin L, Engstrom S, Målstaed S.
Trends in number of consultations and antibiotic prescriptions for respiratory tract infections between 1999 and 2005 in primary healthcare in Kalmar County, Southern Sweden.

III. Neumark T, Brudin L, Mölstad S.
Use of rapid diagnostic tests and choice of antibiotics in respiratory tract infections in primary healthcare-A 6-y follow-up study.
Scandinavian Journal of Infectious Diseases, 2009; Early Online, 1–7.

Watchful waiting in treatment of spontaneously draining acute otitis media in children- an observational study of microbiology and use of antibiotics.
Submitted to Acta Oto-Laryngologica; manuscript ID: SOTO-2010-0072.
# Abbreviations

<table>
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<tr>
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<th>Definition</th>
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<tr>
<td>AOM</td>
<td>Acute Otitis Media</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical Classification System</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>ENT</td>
<td>Ear-Nose-Throat</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>ICD 10</td>
<td>International Classification of Diseases and Related Health problems, 10th version</td>
</tr>
<tr>
<td>KSH 97P</td>
<td>ICD-10 based, primary care adapted classification system</td>
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<tr>
<td>ND</td>
<td>No data</td>
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<tr>
<td>NSAID</td>
<td>Non Steroid Anti Inflammatory Drugs</td>
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<tr>
<td>Otorrhea</td>
<td>Ear secretion</td>
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<td>PCR</td>
<td>Polymerase chain reaction (gene amplification method)</td>
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<tr>
<td>PcV</td>
<td>Phenoxympenilpenicillin, penicillinV</td>
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<tr>
<td>RTI</td>
<td>Respiratory tract infection</td>
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<tr>
<td>SOM</td>
<td>Serous (Secretory) Otitis Media</td>
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<tr>
<td>S.pyogenes</td>
<td>Streptococcus pyogenes, GAS, GABS</td>
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<tr>
<td>β-hemolytic Streptococcus group A</td>
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<td>Strep-A</td>
<td>Rapid diagnostic tests for the detection of S.pyogenes</td>
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<td></td>
<td>(Point of care test for the detection of GABS)</td>
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<tr>
<td>URTI</td>
<td>Upper respiratory tract infections</td>
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<tr>
<td>LRTI</td>
<td>Lower respiratory tract infections</td>
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</table>
INTRODUCTION

Bacteria resistant to antimicrobial treatment have become a worldwide problem, probably because of overuse of antimicrobial drugs. Antibiotic use is related to the emergence and spread of resistance in society - a process based on selection of organisms that have enhanced the ability to survive doses of antibiotics [1-8]. Previously curable disease may become a modern plague.

The rapid increase of resistant *Streptococcus pneumoniae* (*S.pneumoniae*) has been of particular concern, causing problems in the treatment of life-threatening infections as well as common respiratory tract infections (RTIs), such as acute otitis media (AOM).

Most respiratory tract infections are self-limiting. In addition, the majority of studies show that the effect of antibiotics is related not only to the diagnosis and etiologic agent but also to the severity of symptoms. Therefore, general practice (GP) should try to identify those patients that might benefit from antibiotics to optimize the prescribing of antibiotics.

In Sweden, 90% of all antibiotics are prescribed to out-patients and approximately 60% of all prescriptions are prescribed for RTIs [9]. But indications for antibiotic use are often less well defined in the practical, clinical context, and even if defined, the practicing physician’s knowledge may vary. This creates problems when analyzing quality in antibiotic prescribing and whether new national guidelines for the treatment of infections are followed or implemented in general practice.

This thesis is about the management of acute otitis media and respiratory tract infections in Swedish primary care. The emphasis is on AOM, the main reason for prescribing antimicrobials in young children. The thesis tests the method of “wait and see” in the treatment of AOM in an open randomized trial. Furthermore, new knowledge on the natural course of AOM with spontaneous perforation without initial antibiotic intervention is presented. Finally, the thesis examines the management of AOM and RTIs in a defined population over six years.
Introduction

Acute otitis media

Acute otitis media continues to be one of the most common childhood diseases and is a major cause of morbidity in children [10]. By the age of two, up to 70% have had at least one, and every fifth, three or more episodes of AOM [11, 12]. AOM is defined as the presence of middle-ear effusion in conjunction with rapid onset of one or more signs or symptoms of inflammation/infection in the middle ear such as otalgia, otorrhea, fever or irritability [13].

For many years, antibiotics were the only acceptable treatment for AOM due to fear of suppurative complications such as acute mastoiditis. Paracenthesis was an acceptable therapeutic and immediately pain relieving alternative often in combination with antibiotics. According to the Swedish guidelines from 1995 AOM should be treated with antibiotics or paracenthesis [14]. This strategy has since been questioned and several randomized clinical trials and meta-analyses indicated that antimicrobial treatment of AOM might often be unnecessary, even for small children [15-22].

In the year 2000 new Swedish guidelines were developed for the treatment of acute otitis media in children. These guidelines recommended empirical treatment with phenoxymethylpenicillin (PcV) for children under two and over 16 years of age and for those with general distress, underlying disorders or with perforated AOM irrespective of age [23]. Children aged 2-16, were given a non antibiotic treatment alternative, the “wait and see” approach, but the guidelines also offered a second alternative; to give immediate treatment with antibiotics. Thus, the consensus provided two options; immediate antibiotic treatment or the possibility to observe without antibiotics for three days. The document concluded that clinical trials managed under conditions prevailing in Sweden were lacking and asked for a prospective evaluation of the usefulness of PcV, regarding the effect both on patient recovery and on the workload of primary care. This became the starting point for an open randomized study on acute otitis media in children in presented paper I.

Today, many European as well many non-European countries have adopted a “wait and see” strategy in treatment of uncomplicated AOM, irrespective of age in some countries [24]. But immediate antibiotic treatment is still generally recommended in children with perforated AOM, which is in accordance with reviews indicating perforation as a risk factor for complications [25-27]. It has been proposed that the presence of a perforation could be due to bacteria that
are more virulent and consequently a higher risk for complications. However, I could not identify any study, which specifically addressed children with spontaneously ruptured tympanic membranes. This fact was intriguing and incited a prospective observational study of children with AOM with perforation (Paper IV).

Respiratory tract infections

The respiratory tract is the most common site for infections, which are more common in winter. RTIs represent a heterogeneous group of common acute infectious problems and consist of compound diagnoses and symptoms which are sometimes difficult to distinguish from each other. Depending on their location, diseases can be divided into upper (URTI) and lower respiratory tract infections (LRTI). The most common URTIs are common cold, tonsillitis & pharyngitis (sore throat) and sinusitis and LRTI; acute bronchitis and pneumonia. Influenza often affects both upper and lower airways. Acute otitis media maintains a particular position since in Scandinavia AOM is one of the URTI diagnoses. However the diagnosis is sometimes considered to be in a class by itself.

RTIs are most often caused by one or more respiratory viruses such as rhinoviruses, RSV, adenoviruses, influenza, parainfluenza and in some cases by bacteria where the most common are S.pneumoniae, H.influenzae, M.catarrhalis, S.pyogenes and M.pneumoniae.

Children are more susceptible to RTIs than adults. This may, among other things, be due to the not yet attained immunity to the many viruses and bacteria that can cause RTIs and the close person to person contacts due to children’s behavior.
Introduction

Some factors influencing the prevalence of infections in childhood

Impact on vaccinations on otopathogens

Vaccination is generally considered the most efficient and cost-effective method of preventing infectious diseases.

The Swedish National Board of Health and Welfare recommends a vaccination programme for children against defined diseases with appropriate immunization schedules [28]. The program includes immunization against *Hemophilus Influenzae* type b since 1992 for prevention of epiglottitis, septic conditions and meningitis. I have not found any study showing that vaccination against *H.influenzae* may be preventive in AOM in children.

In 2009, a septivalent pneumococcal vaccine was introduced to prevent invasive pneumococcal disease in Kalmar County [29]. This vaccine will soon be replaced by a 13-valent (Prevenar13) vaccine. The pentavalent vaccine covered 75-100% of serotypes causing invasive pneumococcal disease in children below the age of 5 and was found to reduce the incidence of AOM [30, 31]. Black S and al. [32] in the Northern California Kaiser Permanente study found the efficacy of the heptavalent vaccine against clinical AOM episodes was 7% and 89% in all cases of invasive disease. In a prospective, randomized, double-blind study of pneumococcal conjugate vaccine in an unselected population of children in Finland, Escola et al. [33], found that the heptavalent vaccine reduced the number of episodes of AOM of any cause by 6% and Palmu et al. [34] found a reduction of 18% in the proportion of children having experienced multiple events of AOM and a reduction of 39–44% in tympanostomy tube procedures to children from 24 months to 4–5 years of age.

In Sweden the vaccination against seasonal influenza is not included in the vaccination program for children. However the pandemic outbreak of *Influenza A*(H1N1) -“swine influenza” resulted in free of cost vaccination of all citizens including children aged >6 months and may very likely also prevent influenza related AOM- episodes in children [35].
**Introduction**

**Day-care**

The child-care environment predisposes young children for infection with a variety of pathogens [36-39]. Respiratory tract infections as well as gastroenteritis are usually transferred from person to person through close physical contact. In 2006, 85% of all children aged 1-5 and 6-9 years of age, 80% were enrolled in the daycare system in Sweden [40]. Forsell et al. [41] found that children aged 2-5 attending day care centers consulted more and received more antibiotics for RTI (75 vs. 53% and 66 vs. 44%, respectively) compared to children in home and family care. Those findings were in line with another Swedish study [42]. In a Norwegian study, Nafstad et al. [43] found that about 14% of the common cold and 26% of AOM in children aged 3-5 were estimated to be attributable to day care center attendance. In a Dutch meta-analysis of 53 studies, Rovers et al. [44] found strong evidence for an association between attending day-care centers and otitis media.

Determining ways to control infections are good hygiene and health status of both care providers and children including established routines for washing hands, handling toilet visits, meal/food handling, staffing situation (number of staff per child) and routines in managing children with manifest illness [45-47].

**Antimicrobial resistance**

After the introduction of penicillin, *pneumococci* were generally believed to be uniformly sensitive until 1967, when the first strain with decreased susceptibility to penicillin was isolated in Australia [48]. During the following years resistant strains were recovered from humans all over the world [49-52]. Garcia-Martos et al. [53] found that the resistance rate in *pneumococci* to penicillin in Cadiz, Spain was as high as 47% in 1991, 73% in 1993 and 89% in 1995. However, few studies have been performed in general practice and the resistance rates may be lower in the general population [54, 55].

In Sweden, surveillance of resistance has been conducted by the Swedish center for communicable diseases. Selected microbiologic laboratories have taken part in an annual resistance surveillance and quality control (RSQC) program in which they were asked to collect resistance data for defined antibiotics in 100 consecutive clinical isolates of a number of bacterial species. Respiratory tract bacteria have been part of this program every year [56].
The most commonly found serotypes with reduced susceptibility to penicillin in 2008, were the serotypes 19F, 9V, 14, 6B, and 23F [57].

The rate of \textit{S.pneumoniae} with reduced susceptibility to penicillin in Sweden was < 5% for many years (Figure 1)[58]. However, in the early 1990s, the resistance rate in southern Sweden (Skåne County) increased to about 10% [58-60]. Despite a decreasing trend in the use of antibiotics between 1993 and 2004, especially among children, the resistance rate continued to increase. This indicates that once having reached a certain level of resistance in bacterial carriage strains such as \textit{pneumococci}, the problem may not be resolved just by just reducing antibiotic use. But, Guillemot et al. [3] found that intensive educational strategies aimed at optimizing antibiotic use could significantly reduce the penicillin non-susceptible \textit{S. pneumoniae} colonization in areas with high resistance rates.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Antibiotic resistance (R\%) of \textit{Streptococcus pneumoniae} to penicillin’s (I+R ox screen), erythromycin, tetracycline, and co-trimoxazole. Strama 2010 [61]}
\end{figure}
Antibiotic use

The discovery of penicillin and sulfonamides was a breakthrough in the fight against bacteria. As early as 1897, Ernest Duchesne discovered the effect of Penicillium glaucum on some coli bacteria and typhus, but his thesis was rejected by the Faculty of Medicine and Pharmacy of Lyon [62, 63]. Alexander Fleming, became famous for his discovery of penicillin in 1928 [64].

Since the first pioneering efforts from the end of the 19th century the use of antimicrobials was introduced in out-patient care after the Second World War. After penicillin, a large number of antibiotic classes followed in the next 20 years. However, during the last 20 years few new antibiotics have been introduced, which is a major problem in times of increasing resistance. In addition, in many countries, antimicrobials can be obtained without a prescription, even in Europe.

Respiratory tract infections are the most common reason for consulting a GP [65]. During the last decade, studies and reviews have shown that the benefit of antibiotic treatment for most RTIs is limited, affecting symptoms and recovery time only marginally [66, 67]. But physicians frequently prescribe antibiotics especially when they believe patients expect them to, though receiving a prescription is not in itself associated with increased patient satisfaction [68].

The increasing prevalence of resistance in pneumococci incited the formation of Strama (the Swedish strategy against resistance) in 1995 [61]. During the following years a multiprofessional collaboration was set up in regional Strama committees [59, 60]. Strama probably played a major part in the reduction of antibiotic use in Sweden between 1993 and 2005 [69] by an average of 22%, and for children by 50%, Figure 2-4 [70].
Introduction

Figure 2. Antibiotic use in outpatients in Kalmar County, by type (2000–2009). Strama 2010 [61]

Figure 3. Antibiotic use in outpatients in Sweden, by type (1987–2009). Strama 2010 [61]
New guidelines were developed for the treatment of acute otitis media in 2000 [23], acute sore throat in 2001 [71], and acute rhinosinusitis in 2005 [72], urinary tract infections in 2007 [73] and lower RTIs in 2008 [74] which may have influenced antibiotic prescription rates in outpatient care. In some regions a further decrease in antibiotic use was noted [75].

To evaluate the management of infections in primary care in relation to guidelines, knowledge of indications for antibiotic prescription for a population is needed. In Sweden as in most countries, indication-based registers are lacking. Therefore, diagnosis/prescription studies were performed during one week in the year 2000, 2002, and 2005. These studies indicated that antibiotic prescription and the use of rapid diagnostics could be further improved. In addition, the studies indicated that the visiting rates for RTI had declined [9, 69]. However, the results of such short study periods may be influenced by epidemics and can be questioned.

So, further information on the management of infections in primary care was needed. Since data from electronic patient records from Kalmar county was accessible from 1999 to 2006, number of consultations, diagnostic categories, antibiotic prescriptions and the use of rapid diagnostic tests were retrieved and analyzed (Papers II & III) [76, 77].
Near-patient tests and diagnostic uncertainty

The medical history, duration of illness together with clinical findings is sometimes not enough to differentiate between viral or self-limiting bacterial infections and those which may benefit by antibiotic intervention. This diagnostic uncertainty may lead to empirical treatment with antibiotics, which in turn may have also influenced the choice of diagnosis, justifying prescription [78, 79].

In RTIs, near-patient testing methods are widely used in Swedish primary health care [77, 80, 81]. Those most used are rapid diagnostic tests to diagnose *S. pyogenes* (Strep-A) and quantitative determination of C-reactive protein test (CRP). The Strep-A test is an immunoassay for the qualitative detection of group A streptococcal antigen. The specificity and sensitivity in some brands is > 97% (for example; Inverness Medical, Test Pack +Plus) (http://www.testpack.com/index/strep_a/product_specs.aspx). Such high values are, of course highly dependent on the test being properly obtained.

Current Swedish guidelines stress the use of Centor-criteria [82, 83] to select those that might benefit from antibiotics before testing with Strep-A since identification of a pathogen is not enough cause for treatment. When used according to guidelines it may increase appropriate prescription of antibiotics.

CRP is a highly sensitive but not specific systemic marker of inflammation and tissue damage [84, 85]. CRP has been found to be useful to distinguish between viral and bacterial etiology in sinusitis and lower respiratory tract infections, but there are conflicting results concerning the validity of this test [86-90]. Van der Meer et al. [90] concluded after a systematic review that the evidence did not consistently and sufficiently support a wide introduction of CRP-rapid test to guide antibiotics prescription in lower respiratory tract infections. Lagerström et al. [91] found that 41% of patients with radiologic verified pneumonia presented with CRP values <50mg/l and as many as 21% with values <20mg/l and concluded that low CRP levels do not exclude a pneumonia diagnosis in primary care. However, Melbye et al. [92] found that the CRP was the best discriminator between pneumonia and non pneumonia in patients with LRTI symptoms. Lindebaek et al. [93] found, in a Norwegian study, that CRP testing contributed to the diagnosis in 30% of patients with an infectious illness and a reduction in the use of antibiotics in about 25% of consultations.
Hansen et al. [94] found, in a placebo controlled study of acute maxillary sinusitis, that patients with a high degree of sinus pain and increased CRP - levels treated with penicillin V had faster resolution of pain.

The use of rapid diagnostic tests is justified in defined diagnostic situations to improve antibiotic prescription and treatment. But according to Swedish studies, their use was often disproportionate to their therapeutic benefit especially when used on too broad or incorrect indications [81, 95]. Therefore, their use and interpretation need to be followed to improve their use in daily patient care.

**Some explanations for inappropriate prescription habits**

It is well known that patient expectations as well as diagnostic uncertainty may result in inappropriate antibiotic prescription for RTI infections.

Physicians frequently prescribe antibiotics especially when they believe patients expect it, although receiving a prescription is not in itself associated with increased patient satisfaction [68]. Ong et al. [96] interviewed both patients consulting for RTI and the consulted physicians and found that physicians were more likely to prescribe antibiotics to patients who they believed expected them, although they correctly identified only about 25% of those patients. Moro et al. [97] found that diagnostic uncertainty was perceived by pediatricians as the most frequent cause of inappropriate prescription (56% of 633 interviewed). Patient satisfaction was not related to prescribing antibiotics but was related to the belief they had received a better understanding of their illness. Lundkvist et al. [98] showed that the antibiotic prescription rates were lower and patient satisfaction higher when the doctor allocated more time to the consultation. Genevieve Cadeieux et al. [99] followed 852 primary health care physicians during their first 6-9 years of practice in Quebec, Canada (1990-1998) and found that physicians with high practice volumes were more likely to prescribe antibiotics for RTI than those with low practice volumes (RR 1.27, 95% CI 1.09–1.48). She also found that international medical graduates were more likely than University of Montréal graduates to prescribe antibiotics for viral respiratory infections (risk ratio [RR] 1.78, 95% confidence interval CI 1.30–2.44). In a Norwegian study from 1996, Strand and al. [100] found that GPs working on fee-for-service basis
Introduction

seemed to prescribe more broad spectrum antibiotics, regardless of the therapeutic guidelines. In a study from UK, Little at al. [101] found that perceived pressure from patients was a strong independent predictor of whether doctors examine, prescribe, refer, or investigate.

So, many non-medical reasons influence decisions to prescribe an antibiotic for an RTI. But in conclusion, most studies indicate that patient satisfaction relies more on a careful clinical examination and a good explanation of their condition than on a prescription of antibiotics [98, 102-105].
AIMS OF THE PRESENT INVESTIGATIONS

- To evaluate the possible benefits of PcV treatment as compared to an “wait and see” policy in the treatment of uncomplicated AOM in children aged 2-16 years in primary care

- To evaluate the healing process of AOM with spontaneously ruptured tympanic membranes in children aged 2-16 without interference of antibiotic treatment

- To analyze the management of AOM and respiratory tract infections in primary care in Kalmar County 1999-2005

- To evaluate changes in the number of visits, diagnoses, and antibiotic prescriptions for RTI in primary healthcare in Kalmar County during 1999-2005

- To evaluate changes in treatment of different RTIs for different age groups and the use of rapid diagnostic tests in relation to Swedish guidelines during 1999-2005
PATIENTS AND METHODS

This thesis is based on four investigations using data acquired from

- a prospective, randomized, open study on patients aged 2-16 consulting primary health care with AOM (I)
- a prospective, observational clinical follow-up study on patients aged 2-16, presenting with AOM with spontaneous perforation, without initial use of antibiotics (IV)
- retrospective, descriptive, population-based studies of electronic patient records concerning 240,447 patients visiting primary health care units in Kalmar County for an RTI between 1999 and 2005 (II & III)

Short summary of main study characteristics

<table>
<thead>
<tr>
<th>Paper</th>
<th>Year of data collection</th>
<th>Study population</th>
<th>Data sources</th>
<th>Method</th>
<th>Level of assessment</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>2002-2004</td>
<td>179 patients aged 2-16, consulting GP with AOM</td>
<td>Clinical consultations, patient diaries</td>
<td>Randomization, phone follow-up, final clinical control</td>
<td>Symptom duration, frequency of complications (up to three months), consumption of healthcare services</td>
</tr>
<tr>
<td>II</td>
<td>1999-2005</td>
<td>240,447 consultations with RTI</td>
<td>Electronic patient records</td>
<td>Data extraction</td>
<td>RTI diagnoses, antibiotic prescriptions, age groups</td>
</tr>
<tr>
<td>III</td>
<td>1999-2005</td>
<td>240,447 consultations with RTI</td>
<td>Electronic patient records</td>
<td>Data extraction</td>
<td>RTI diagnoses, choice of antibiotics, the use of rapid diagnostic tests, age groups</td>
</tr>
<tr>
<td>IV</td>
<td>2007-2009</td>
<td>72 patients aged 2-16 with AOM and spontaneous perforation of the eardrum</td>
<td>Clinical consultations, patient diaries</td>
<td>Diagnostic visit, 3 follow up’s</td>
<td>The need of antibiotics due to persisting AOM within 9 days. Bacteriology, appearance of tympanic membrane and aural secretion. New AOM and SOM within 3 months</td>
</tr>
</tbody>
</table>
Patients (Paper I)

The study was performed at 32 primary health care centers in the county of Kalmar (20), Jönköping (10) and Östergötland (2), involving 72 general practitioners (GPs). All participating GPs were familiar with the use of aural microscopic equipment to ensure optimal diagnostic accuracy. From October 2002 to May 2004, children 2-16 years old meeting the inclusion criteria were consecutively included in the study. The diagnosis was based on history and direct inspection of the ear drum which had to appear bulging or red displaying reduced mobility. Patients in need of antibiotics for other reasons, recurrent AOM (three or more episodes of AOM during the past six months), immunosuppressive conditions, genetic disorders, and mental disease or retardation were not included.

Patients (Papers II & III)

These retrospective studies were based on data extracted from the database of the patient record system “Swedestar”. The data extracted represented all physician visits performed for the RTI diagnoses in primary care in Kalmar County from 1999 through 2005. In the middle of the study period (31 December 2002), the population of Kalmar County comprised 234,627 individuals, 118,070 women and 116,557 men [40].

Patients (Paper IV)

The study was conducted between February 2007 and May 2009 at participating ENT-clinics in the hospitals of Kalmar, Eksjö, Nässjö and two private ENT-clinics in Malmö. All primary health centers situated in the neighborhood of the participating ENT-clinics were informed of the study. When contacted by phone (patient are, except in emergency situations, always recommended to contact their primary health care provider by phone before visiting) the health centers agreed to refer children aged 2-16 with an ear discharge and symptom duration of less than 4 days.

Seventy-two patients who met the inclusion criteria, presenting with single or double-sided AOM with spontaneous eardrum perforation, were included.
Results

Not included were children with grommet, chronic ear conditions or impaired hearing, concurrent disease that should be treated with antibiotics, recurrent AOM (three or more episodes of AOM during the past six months) or immunosuppressive conditions.

Method (Paper I)

At inclusion, patient data on participating patients were registered in predesigned study forms. Included patients were randomized by an Internet-based, random number generator to treatment with PcV 25 mg/kg x 2 for five days (according to Swedish guidelines) or no antibiotic treatment [23]. A checklist for diagnostic inclusion criteria, symptom duration and outcome of randomization procedure had to be filled in. Guardians were carefully instructed to reconsult in case of non-improvement or deterioration within three days after randomization. Patients who met the inclusion criteria but did not accept the randomization procedure were asked to participate in the follow-up but with their own treatment choice. These patients were excluded in the reported analysis in paper I.

Patient diary
All participants registered number of doses of given medications, fever, sleeping disturbances, rash, vomiting, diarrhea, absence from day-care/school, and the day they appraised that the condition of their child was back to normal, and symptoms such as pain, in a diary in a semi-structured way on a daily basis (0-no pain, 1-some, 2-moderate, 3-severe). The diaries were returned to the primary care center after one week.

Follow-ups
A nurse telephoned all participants after approximately 14 days to supplement information in the diary and follow up all acute contacts that had occurred during the first week of treatment. The final follow-up was performed after three months and perforations and serous otitis media were registered. This consultation also included information on healthcare contacts during the last three months. Patients who did not show up at the three-month follow up were interviewed by telephone. Symptomatic treatment with paracetamol or NSAIDs, drugs reducing the swelling of the nasal mucosa (e.g. xylomethazolin), and nasal steroids were allowed.
The Medical Product Agency performed a final control validating collected data.

**Method (Papers II & III)**

The database of the electronic patient record system Swedestar was accessible online, allowing extraction and analysis of patient data. All patients visiting the primary health care center were registered in the patient data system and identified by their social security numbers. The registration of diagnoses using a primary care adapted, ICD-10 based classification system [106, 107], was compulsory. Registration of diagnoses was performed exclusively by physicians. When using the integrated drug-prescribing module, all drugs were automatically registered according to the Anatomical Therapeutic Chemical Classification System [108].

All GP consultations (office and out-of-office hours), receiving an RTI diagnosis according to the current classification code were included and the database comprised 240,447 consultations for an RTI.

The following data was extracted from electronic patient records: date of consultation, age, gender, diagnosis, and antibiotics prescribed (ATC-code) and, in study III, number and results of diagnostic tests used (CRP, Strep-A).

Data was extracted quarterly from July 1999 to December 2005 and further presented from July to June to avoid the influence of viral epidemics.

For selected analyses in paper II, common cold, pharyngitis, tonsillitis, AOM, sinusitis, and laryngitis were grouped together as upper respiratory tract infections and influenza, acute bronchitis, and pneumonia as lower respiratory tract infections. The diagnoses in study III are otherwise accounted for separately.

**Data collection and rectification (Papers II & III)**

The data was downloaded by individual access to the respective database of each primary health care unit in Kalmar County. All data was initially collected using Microsoft Excel 2007. Rare diagnoses or combined diagnoses with a consultation frequency lower than 1000 of the 240,447 included consultations were classified as “others”. Similarly, rare antibiotics and less common combinations were considered together.
Results

The process of rectification and categorization began with the reduction of a total of 1979 different ways of describing combinations of diagnoses to 102 and finally to nine single diagnoses. In the report, only one diagnosis was allowed per consultation so that all diagnoses were ranked after severity and in combination, the most “severe” diagnosis being selected. For example, if one patient had the diagnoses AOM, common cold and acute bronchitis, that consultation was reentered as AOM. The Strep-A test results were often misspelled and entered incorrectly. In doubtful cases, results were classified as no data (ND). During the rectification if the extracted data was considered incorrect, patient record were examined for verification. After rectification analyses were performed using StatSoft-Statistica v7.1.

Method (Paper IV)

The patients were taken care of by otolaryngologists and one experienced resident physician. After clinical examination swabs for microbiologic investigations were collected from the nasopharynx and ear secretions. At inclusion the presence of infectious symptoms, the duration of discharge and duration of ear symptoms were recorded in study forms. The appearance of both eardrums and different qualities of the secretion were documented. None of the children received antibiotic treatment at inclusion.

Patient diary

All participants were asked to register their experienced pain daily for seven days (0-no pain; 1-some, 2-moderate, 3-severe pain), number of doses of prescribed analgesics, fever, sleep disturbances, duration of discharge, cough, sore throat, absence from day-care/school or sick-leave, and the day parents considered the condition of their child back to normal (recovery day). The diaries were returned at the second follow-up visit (day 7-9).

Follow-ups

The children were further clinically assessed after 2-4 days, 7-9 days and three months after inclusion. Terracortril with Polymyxin B eardrops was allowed in case of external otitis but only after the first follow-up. Antibiotic treatment was considered in absence of improvement or increasing symptoms or other
infections. If antibiotic treatment was required at follow-up, the patient only participated in the final control after three months. At the follow-up visits the status of the tympanic membrane and amount and quality of secretions were documented. In connection with the final control after three months, information about all healthcare contacts during the study period was gathered.

**Microbiological specimens**

Microbiological specimens for culture and PCR were collected using nasopharyngeal swabs. Cultures were performed with established routine methods. PCR investigations of middle ear secretions were performed at the Dept of Clinical Microbiology, Lund University Hospital. PCR was performed using real-time assays for *Haemophilus Influenzae (H.influenzae)* [109], *Moraxella catarrhalis (M.catarrhalis)* [110], *Mycoplasma pneumoniae (M.pneumoniae)* [111], *Chlamyphila pneumoniae (C.pneumoniae)* [112], *Fusobacterium nucleatum-periodonticium-russii* [113], and *F.necrophorum* [114]. For *Alloicoccus otitidis (A.otitidis)* and *Streptococcus pneumoniae (S.pneumoniae)* in-house Taqman assays targeting the highly specific regions of 16S rDNA [115] and *lytA* [116], respectively, were applied. *S.pyogenes* was not detected using PCR, because a suitable method was not established but the established routine culture technique was considered to have high sensitivity.

**Statistical methods**

In paper I, all patient variables were manually transferred from the study questionnaires to a Microsoft Access 2003 database henceforth processed in Excel 2003 and finally analyzed in StatSoft- Statistica v7.1

In Papers II & III, extraction of data from the Swedstar databases was performed using Visual Basic based tools (generator) and loaded into Microsoft Excel 2007 spreadsheets and all data was analyzed in Statistica. In the fourth study described in paper IV, all data from the study questionnaires were manually transferred to Excel 2007 and analyzed in Statistica.
Results

In papers I-IV, most data was descriptive and units are described in figure legends and tables. In paper I and IV, differences between more than two groups were analyzed using a chi-squared test for proportions if not otherwise stated (followed by Fisher’s exact test in the case of significance) and nonparametric tests for continuous variables (Kruskal-Wallis test followed by Mann-Whitney U-test in the case of significance). In the case of two groups, Fisher’s exact test was used for proportions and a Mann-Whitney U-test for continuous variables.

Trends in paper II were analyzed by linear regression analysis using logarithmic data on counts (number of visits) as the dependent variable, and quarters of years (from third quarter 1999 to last quarter 2005; n=26) as the independent variable.

In paper IV, the association between eardrum status and secretion type on the one hand and antibiotics (yes/no) during the study period was analyzed using discriminant analysis and presented as receiver operating characteristic (ROC) curves. A p-value of <0.05 was considered statistically significant.

Background information about population size, composition and changes over time was obtained from Statistics Sweden (Statistiska centralbyrån) available at [40] http://www.scb.se/Pages/SubjectArea_2442.aspx. The list size of participating health care center was obtained from Kalmar County council and the prescription statistics of antibiotics in Sweden from Strama [61].

Ethics: All studies were approved by the Ethical Committee in Linköping.
RESULTS

Acute otitis media

In paper I, 179 patients aged 2-16 presenting with AOM were randomized to either treatment with PcV or treatment without the use of antibiotics. There was no significant difference between the groups in the cumulative number of recoveries day by day (p=0.606). The median recovery day was day four in both groups and approximately 80% had recovered on day seven (Figure 5).

Figure 5. The cumulated number of patients by parents reported as recovered according to parent’s diary records
**Results**

**Table 1.** Follow up variables in terms of phone contacts, new appointments, risk for long term complications and economic implications

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PcV</th>
<th>no PcV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone contacts day 1-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total phone contacts (mean (range))</td>
<td>0.1 (0-1)</td>
<td>0.2 (0-3)</td>
<td>0.603</td>
</tr>
<tr>
<td>New urgent appointments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-specific; day 1-7 (n; %)</td>
<td>4 (4%)</td>
<td>13 (15%)</td>
<td>0.021</td>
</tr>
<tr>
<td>All; day 1-7 (n; %)</td>
<td>4 (4%)</td>
<td>16 (18%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Treatment failure / perforation; day 2-7 (n; %)</td>
<td>0 (0%)</td>
<td>4 (5%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Disease-specific; 0.5-3 months</td>
<td>9 (10%)</td>
<td>10 (13%)</td>
<td>0.808</td>
</tr>
<tr>
<td>Planned follow up (14 days &amp; 3 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered at day 14 (n; %)</td>
<td>71 (82%)</td>
<td>70 (85%)</td>
<td>0.541</td>
</tr>
<tr>
<td>Perforation after 3 months</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Serous otitis media after 3 months</td>
<td>10 (12%)</td>
<td>8 (11%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Subjective recovery after 3 months</td>
<td>73 (85%)</td>
<td>63 (84%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Economic aspects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents at home (n; % of all)</td>
<td>49 (56%)</td>
<td>42 (53%)</td>
<td>0.755</td>
</tr>
<tr>
<td>Days home from work (median (range))</td>
<td>1.2 (0-7)</td>
<td>1.2 (0-7)</td>
<td>0.904</td>
</tr>
</tbody>
</table>

Children randomized to PcV were relieved from moderate to severe pain (pain score 2-3) on average 0.4 days earlier compared with children randomized to treatment without antibiotics (p<0.001) (Paper I). The use of analgesics during days 1-3 (expressed as number of children given analgesics day by day) as well the median number of doses of analgesics during day 1-7 was significantly higher among children randomized to no antibiotics (p<0.001).

The number of new consultations for symptoms related to AOM during the first week, such as perforations at days 0 and 1, ear discomfort, and hearing disturbance, was significantly higher in children randomized to no antibiotics (15%) than among children randomized to PcV (4%) (p<0.021). There were no significant differences in the occurrence of treatment failures, perforations or in the prevalence of serous otitis media (SOM) after three months. The number of phone contacts with the primary health care centre and the number of days a parent stayed home from work to take care of their child were also similar (Table 1).
Epidemiology of AOM (Papers II & III)

Between January 2000 and December 2005, corresponding to six complete infectious seasons, 27 077 (12% of all RTI diagnoses) patient visits were diagnosed as AOM (Paper II). Children aged 0-6 consulted proportionally most and the diagnosis AOM accounted for 271 visits/ 1000 inhabitants aged 0-6. Children aged 2–16 yrs. showed decreasing yearly consultation rates between 2000 and 2005 by almost 10% (Figure 6), but the relative number receiving antibiotics was fairly constant over the years, on average 76%. PcV accounted for 78% of all antibiotics prescribed.

Figure 6. Number of visits and antibiotic treatment for acute otitis (AOM) in children 2000-2005. Note the number of visits as well as antibiotic prescriptions dropped drastically in the age group 2-16 after 2002

AOM with perforation

In the second clinical trial described in paper IV, 72 children aged 2-16 years presenting with AOM complicated by spontaneous perforation were included. The main findings at the day of inclusion are presented in Table 2.
Results

Table 2. Upper section: Ear status. Ear1 is the affected ear and ear2 is the contra lateral side (note that 2 subjects in each age class had bilateral otitis rendering inclusion. Intermediate section: Duration of symptoms (days). Lower section: Number of individuals (%) with specific symptoms

<table>
<thead>
<tr>
<th>Tympanic membrane appearance</th>
<th>&lt;4 yrs (N=37)</th>
<th>≥4 yrs (N=35)</th>
<th>Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin patches</td>
<td>Ear1 n(%)</td>
<td>Ear2 n(%)</td>
<td>Ear1 n(%)</td>
</tr>
<tr>
<td></td>
<td>28 (76)</td>
<td>1 (3)</td>
<td>31 (89)</td>
</tr>
<tr>
<td>Bulging eardrum</td>
<td>14 (38)</td>
<td>6 (16)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Pulsating secretion</td>
<td>7 (19)</td>
<td>3 (8)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Bulla formation</td>
<td>8 (22)</td>
<td>2 (5)</td>
<td>8 (23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secretion type-otorrhea</th>
<th>&lt;4 yrs (N=37)</th>
<th>≥4 yrs (N=35)</th>
<th>Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purulent secretion</td>
<td>Ear1 n(%)</td>
<td>Ear2 n(%)</td>
<td>Ear1 n(%)</td>
</tr>
<tr>
<td></td>
<td>25 (68)</td>
<td>2 (5)</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Abundant secretion</td>
<td>6 (16)</td>
<td>2 (5)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Spacing secretion</td>
<td>28 (76)</td>
<td>0 (0)</td>
<td>25 (71)</td>
</tr>
<tr>
<td>Serosanguinous</td>
<td>8 (22)</td>
<td>0 (0)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Dried secretion</td>
<td>15 (41)</td>
<td>0 (0)</td>
<td>13 (37)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other findings</th>
<th>&lt;4 yrs (N=37)</th>
<th>≥4 yrs (N=35)</th>
<th>Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhagic secretion</td>
<td>Ear1 n(%)</td>
<td>Ear2 n(%)</td>
<td>Ear1 n(%)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General conditions</th>
<th>n(%)</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral ear with secretion</td>
<td>2 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (57)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Fever</td>
<td>14 (38)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>30 (81)</td>
<td>31 (89)</td>
</tr>
</tbody>
</table>

Footnotes to table
*) Difference of ear 1 between the two age groups (ear 1 in the upper section).
Fisher’s exact test for frequencies and Mann-Whitney U-test for durations.

Twelve patients (17%) were prescribed antibiotics at the first and second follow-up visit (day 2-9) due to lack of improvement and seven between day 16 and 3 months due to a new AOM. Children who received antibiotics had significantly more pain (pain score 2-3) during day one (p=0.003), as well as a higher consumption of analgesics (p<0.001). There was no difference in the mean number of days with pain severity 2-3 during the first week (p=0.023). Median recovery time was 3.9 days in patients without antibiotic intervention and 7.1 days (p=0.002) among those who received antibiotics (Table 3). All
participants except one, who developed an acute mastoiditis possibly due to non-compliance with study protocol, were recovered on day 8.

One recurrent AOM (new perforation) occurred between the second follow-up visit and 30 days ahead. The number of patients who developed a new AOM as the number of patients with SOM after 3 months was somewhat lower (although not significantly so) in patients who had received antibiotics compared to those who had not (p = 0.276 and p = 0.270, respectively (Fishers exact test)).
### Table 3. Follow-up variables during the first week in terms of pain, fever, and early recovery. Days within 10% of patients in every group are not shown separately but as maximum number per day (%) during the remaining days. Analyzed by Fisher’s exact test for proportions, otherwise Mann-Whitney’s U-test.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment strategy</th>
<th>No ab ≤ 9 days (n=56)</th>
<th>ab ≤ 9 days (n=12)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain severity 2-3 (n; %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>15 (29%)</td>
<td>6 (55%)</td>
<td>0.161</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1 (2%)</td>
<td>4 (36%)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>1 (2%)</td>
<td>3 (30%)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Day 3-7 (max)</td>
<td>3 (6%)</td>
<td>2 (20%)</td>
<td>0.227</td>
<td></td>
</tr>
<tr>
<td>Mean # days (range) with pain severity 2-3</td>
<td>0.4 (0-2)</td>
<td>1.5 (0-5)</td>
<td>0.023</td>
<td></td>
</tr>
</tbody>
</table>

| **Analgesics (Yes; n; %)**      |                    |                        |                   |          |
| Day 0                           | 22 (44%)           | 9 (82%)                | 0.043             |
| Day 1                           | 11 (22%)           | 10 (91%)               | <0.001            |
| Day 2                           | 6 (12%)            | 4 (36%)                | 0.067             |
| Day 3                           | 7 (14%)            | 2 (20%)                | 0.633             |
| Day 4-7 (max)                   | 5 (10%)            | 2 (20%)                | 0.322             |
| Mean (range) # of dosis day 1-7 | 1.1 (0-14)         | 4.2 (0-16)             | <0.001            |

| **Fever>38°C (n; %)**           |                    |                        |                   |          |
| Day 0                           | 7 (16%)            | 2 (22%)                | 0.635             |
| Day 1                           | 3 (7%)             | 2 (22%)                | 0.173             |
| Day 2                           | 1 (3%)             | 1 (11%)                | 0.337             |
| Day 3-7 (max)                   | 0 (0%)             | 1 (13%)                | 0.143             |
| Mean # days (range) of fever 1-7| 0.1 (0-2)          | 0.6 (0-5)              | 0.496             |

| **Recovery (%cumulative)**      |                    |                        |                   |          |
| Recovered day 8                 | 45 (100)           | 6 (100)                | -                 |
| Missing                         | 11                 | 6                      | -                 |
| Median (range) recovery day (1-8)** | 3.9 (0-9) | 7.1 (3-9) | 0.002 |

Footnotes to table:

* Fisher’s exact test (categorical parameters) and Mann-Whitney’s U-test (continuous parameters).
** 9 means > 8 days
Results

**Microbiology findings in middle ear secretion (Paper IV)**

Positive cultures or positive PCR were recorded in 36 patients (58%) from the auditory canal and in 68 patients (80%) from nasopharynx. *A. otitidis* was the most frequently identified bacteria from the auditory canal and was found in 23 (34%) patients, *S. pneumoniae* in 12 (18%), *S. pyogenes* in (9%), *M. catarrhalis* in six (9%) and *H. influenzae* in five (7%). The bacterial findings in nasopharynx consisted mostly of *S. pneumoniae* isolated mixed in 41 patients, *M. catarrhalis* in 27, *H. influenzae* in 23 and *S. pyogenes* in 8. Fusobacterium nucleatum was found in five patients while *M. pneumoniae*, *C. pneumoniae* and *Fusobacterium necrophorum* could not be detected.

All patients with presence of *S. pyogenes* in aural secretions received antibiotics compared with one of fifteen with pure isolate of *A. otitidis*. PCR from otorrhea was found to have 50% higher sensitivity (detection rate) (85% versus 44%) as compared to bacterial cultivation and 20% of bacterial growth from nasopharynx was recovered in aural secretion.

**Clinical findings as predictors of antibiotic treatment (Paper IV)**

The most common macroscopic eardrum appearance was characterized by “keratin patches” (n=25; 37%) and “bulging and keratin patches” (n=12; 18%) (Appendix; Photo 1 & 3). In these conditions, the most frequently identified bacterium was *A. otitidis*. The classification of possible secretion findings were dominated by the combination “purulent and sparse” and “purulent and abundant” which was found in 16 respective 12 patients. The combination “purulent and sparse” was associated with presence of *A. otitidis* and *S. pneumoniae*, while *S. pyogenes* dominated in “purulent and abundant” with highest early (day 2-4) antibiotic prescription rate (Table 4). No patients with dried / sparse secretion at inclusion were prescribed antibiotics day 2-9. All patients with presence of *S. pyogenes* received antibiotics.

The constellation with abundant and purulent secretion in addition to pulsating tympanic membrane and absence of keratin patches had acceptable sensitivity and specificity to predict absence of improvement or antibiotic prescribing at follow-up visits (Figure 7).
Figure 7. Forecast of antibiotic treatment during the follow-up period using eardrum status and secretion type. ROC curve showing the sensitivity and specificity corresponding to different choices of cut-offs for the calculated indices of ear drum status, type of secretion and a combination of these (composite index) at the day of admission regarding the expected need of antibiotic treatment within the follow-up period. The x-axis could be regarded as the prevalence of the expected need of antibiotic treatment before ear examination (pre-test) and the y-axis corresponding number after examination (post-test) if index is positive. A positive composite index will e.g. increase the expected need for antibiotics by a factor of >4 if the pre-examination prevalence is 20%.
Ear drum status and type of secretion associated with bacteria species correlated with antibiotic intervention. Groups with two or less individuals are lumped together (others) except for H.influenzae and M.catarrhalis Values within parenthesis represent the number of all patients with the specified bacteria, including all combinations

<table>
<thead>
<tr>
<th>Drum Status</th>
<th>No. pathogens</th>
<th>A.otitidis</th>
<th>S.pneum</th>
<th>S.pyogen</th>
<th>F.nucleat</th>
<th>H.influ</th>
<th>M.catarrh</th>
<th>Others</th>
<th>Antibiotics up to 3 months</th>
<th>Antibiotics day 2-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin patches</td>
<td>9</td>
<td>7 (8)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1 (3)</td>
<td>3</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Iling / Keratin patches</td>
<td>4</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>3</td>
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</tr>
<tr>
<td>Esating</td>
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<td>0 (0)</td>
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<td>0 (2)</td>
<td>1 (3)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Iling / Keratin patches / lla formation</td>
<td>3</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Ratin patches / Bulla formation</td>
<td>3</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
<td></td>
<td>4</td>
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<td>Iling / Bulla formation</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Isating / Bulla formation / ratin patches</td>
<td>0</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td>Totals</td>
<td>26</td>
<td>15</td>
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<td>3</td>
<td>2</td>
<td>2</td>
<td>12</td>
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<td>Secretion type</td>
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<tr>
<td>Purulent/Sparse</td>
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<td>6 (7)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>0 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Purulent/Abundant</td>
<td>1</td>
<td>2 (5)</td>
<td>0 (3)</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>0 (1)</td>
<td>1 (2)</td>
<td>4</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Rosanguardious / Dried sparse</td>
<td>1</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Rosanguardious /Sparse ed/Sparse</td>
<td>5</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Rulent/ Dried /Sparse ed</td>
<td>3</td>
<td>2 (3)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic / Rosanguardious /Sparse</td>
<td>3</td>
<td>1 (2)</td>
<td>0 (2)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (2)</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Totals</td>
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<td>15</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>12</td>
<td>68</td>
<td>12</td>
</tr>
</tbody>
</table>
Results

Respiratory tract infections

Visits

A total of 240,447 consultations for an RTI diagnosis were registered between July 1, 1999, and December 31, 2005, corresponding to 257 consultations/1000 inhabitants per 12-month period (Paper II). Children aged 0–6 yrs consulted proportionally most, with an average of 905 visits/1000 inhabitants of the same age group, where common cold accounted for 366 visits and sore throat for 118. Adults aged 18–44 yrs. had an average of 231 visits/1000 inhabitants of the same age group, most often for common cold (76 visits), followed by sore throat (64 visits, where tonsillitis accounted for 44) and sinusitis (33 visits), (Paper III). Consultations for acute tonsillitis & pharyngitis (sore throat), AOM and laryngitis decreased significantly (p<0.008) during the study period. The decline in the number of consultations for sore throat (acute tonsillitis plus pharyngitis) comprised all age groups (Paper III).

Figure 8. Trends from July 1999 to Dec 2005 of number of physician visits calculated for the most common respiratory tract infections from July 1999 to Dec 2005. The sum of all diagnoses is shown on the right scale, individual diagnoses on the left.
Common cold was the most frequent diagnosis in all age categories except for the oldest (>74 yrs.), where pneumonia dominated. There were large seasonal fluctuations of consultations with peaks during the periods December to May (Figure 8). Similar fluctuations were observed for the prescribing of antibiotics (Figure 9).

**Antibiotic prescriptions**

PcV was the most prescribed antibiotic and accounted for 60% of 107 990 antibiotic prescriptions and doxycycline was the second most prescribed antibiotic with 19 556 prescriptions (Paper III).

![Figure 9. Trends from July 1999 to Dec 2005 of number of physician visits calculated for the most commonly used antibiotics from July 1999 to Dec 2005. No antibiotics represent consultations where no antibiotic was prescribed.](image)

The total number of antibiotic prescriptions decreased by 33% between 1999 and 2005. Antibiotics were prescribed to 41% of children aged <7 yrs. Older children aged 7-17 and adults received antibiotics in about 46% of visits (Paper II). The percentage of PcV was higher in the age groups 0-6 (69%), 7-17 (77%), and 18-44 (65%) and lower in the age groups 45-64 (43%), 65-74 (35%), and >75 (34%) (Paper II)(Table 6). Doxycycline was more often prescribed after the age of 65. Amoxicillin or amoxicillin combined with clavulanic acid (Spekramox®) were most often used in the age group 0-6 (4% and 2%,
respectively). During the study period, the use of all antibiotic classes except doxycycline decreased significantly particularly in patients under 44 (Table 6).

**Antibiotics and diagnoses**

Most antibiotics were prescribed for tonsillitis, AOM, sinusitis, pneumonia and acute bronchitis. Sixty-five percent of consultations for sore throat received antibiotics, primarily PcV (82%) (Table 5, Figure 10) and about sixty percent of patients consulting for bronchitis and pneumonia received antibiotics, mostly doxycycline (Table 5, Figure 11).

In sore throat the relative number of antibiotic prescriptions in all age groups decreased from a total average of 73% (2000–2002) to 64% (2003–2005).

**Table 5.** Diagnoses ranked after severity (except “others”) and antibiotic (ab) treatment (including no ab (noAb)). Sore throat=Tonsillitis & Pharyngitis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>noAb</th>
<th>PcV</th>
<th>Doxy</th>
<th>Erytro</th>
<th>Amox</th>
<th>Cepha</th>
<th>Am+Clav</th>
<th>Others</th>
<th>Tot.(%)</th>
<th>Tot.(abs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>41%</td>
<td>22%</td>
<td>19%</td>
<td>7%</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
<td>100%</td>
<td>14697</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19%</td>
<td>51%</td>
<td>18%</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>100%</td>
<td>19501</td>
</tr>
<tr>
<td>AOM</td>
<td>24%</td>
<td>59%</td>
<td>1%</td>
<td>4%</td>
<td>6%</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
<td>100%</td>
<td>29596</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>17%</td>
<td>68%</td>
<td>0%</td>
<td>4%</td>
<td>1%</td>
<td>6%</td>
<td>0%</td>
<td>3%</td>
<td>100%</td>
<td>31928</td>
</tr>
<tr>
<td>Influenza</td>
<td>92%</td>
<td>4%</td>
<td>3%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>100%</td>
<td>2218</td>
</tr>
<tr>
<td>Ac.bronchitis</td>
<td>40%</td>
<td>12%</td>
<td>33%</td>
<td>6%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>100%</td>
<td>23867</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>66%</td>
<td>13%</td>
<td>12%</td>
<td>2%</td>
<td>4%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>100%</td>
<td>1235</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>75%</td>
<td>19%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>100%</td>
<td>13696</td>
</tr>
<tr>
<td>Com. Cold</td>
<td>84%</td>
<td>8%</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>100%</td>
<td>79751</td>
</tr>
<tr>
<td>Others</td>
<td>86%</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>100%</td>
<td>23956</td>
</tr>
<tr>
<td>Total</td>
<td>55%</td>
<td>27%</td>
<td>8%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>100%</td>
<td>23956</td>
</tr>
<tr>
<td>All Grps</td>
<td>132455</td>
<td>64864</td>
<td>19556</td>
<td>7763</td>
<td>6475</td>
<td>3633</td>
<td>2053</td>
<td>3646</td>
<td>240445</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>35%</td>
<td>53%</td>
<td>0,6%</td>
<td>4%</td>
<td>1,0%</td>
<td>4%</td>
<td>0,3%</td>
<td>2%</td>
<td>100%</td>
<td>45624</td>
</tr>
<tr>
<td>Age Group</td>
<td>No Antibiotics</td>
<td>Penicillin V</td>
<td>Doxycycline</td>
<td>Erythromycin</td>
<td>Amoxicillin</td>
<td>Cephalosporin</td>
<td>Amox+Clavul.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Δ/yr</td>
<td>r</td>
<td>p</td>
<td>%Δ/yr</td>
<td>r</td>
<td>p</td>
<td>%Δ/yr</td>
<td>r</td>
<td>p</td>
<td>%Δ/yr</td>
<td>r</td>
</tr>
<tr>
<td>0-6</td>
<td>-4.5</td>
<td>-0.27</td>
<td>0.181</td>
<td>-7.8</td>
<td>-0.51</td>
<td>0.008</td>
<td>-3.6</td>
<td>-0.40</td>
<td>0.043</td>
<td>1.4</td>
</tr>
<tr>
<td>7-17</td>
<td>-9.4</td>
<td>-0.53</td>
<td>0.005</td>
<td>-12.6</td>
<td>-0.75</td>
<td>0.000</td>
<td>-8.8</td>
<td>-0.77</td>
<td>0.000</td>
<td>-4.7</td>
</tr>
<tr>
<td>18-44</td>
<td>-12.5</td>
<td>-0.47</td>
<td>0.016</td>
<td>-12.0</td>
<td>-0.48</td>
<td>0.013</td>
<td>-11.6</td>
<td>-0.72</td>
<td>0.000</td>
<td>-6.2</td>
</tr>
<tr>
<td>45-64</td>
<td>-10.7</td>
<td>-0.47</td>
<td>0.015</td>
<td>-14.5</td>
<td>-0.70</td>
<td>0.000</td>
<td>-8.0</td>
<td>-0.51</td>
<td>0.007</td>
<td>1.4</td>
</tr>
<tr>
<td>65-74</td>
<td>-22.5</td>
<td>-0.79</td>
<td>0.000</td>
<td>-11.7</td>
<td>-0.66</td>
<td>0.000</td>
<td>-15.2</td>
<td>-0.80</td>
<td>0.000</td>
<td>-6.6</td>
</tr>
<tr>
<td>&gt;74</td>
<td>-19.2</td>
<td>-0.64</td>
<td>0.000</td>
<td>-13.4</td>
<td>-0.53</td>
<td>0.006</td>
<td>-10.9</td>
<td>-0.41</td>
<td>0.039</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Table 6. Changes over time in number of prescriptions of antibiotics in the various age groups. “No antibiotics” represent consultations where an antibiotic was not prescribed.

To Table 6. Bold marked correlations are significant at p < 0.05; %Δ/yr = Relative yearly change (%) during the observation period 1999-2001. *Coefficient. All statistically significant trends are de facto decreasing (negative %Δ/yr values (slopes)). Doxycycline in age group 0-6 not calculated.
Figure 10. Number of visits and antibiotic treatment for sore throat 2000-2005 for the various age groups. Note the decrease in frequencies of sore throat as well as decrease in number of antibiotic prescriptions most evident up to age 44.
Figure 11. Number of visits and antibiotic treatment for acute bronchitis 2000-2005 for the various age groups
Rapid diagnostic tests

The use of rapid diagnostic tests for C-reactive protein (CRP) and detection of β-haemolytic Streptococcus group A (Strep-A) was widespread in Kalmar County. The number of Strep-A tests performed was almost constant over the years. When performed, 60% of patients received the diagnosis sore throat and 18% common cold (Table 7). The number of Strep-A tests performed in patients who received a diagnosis of common cold declined by over 50% from 29% to 14% (2000→2005).

Table 7. Treatment with antibiotics (% ab; bolded) related to outcome of Strep-A-test calculated for sore throat and common cold 2000-2005. ND = Strep-A not done. Total N is number of visits. nS (%) is number of Strep-A tests expressed as % of number of visits calculated for positive and negative results separately. /1000 inh. is Total N converted to the yearly number of listed inhabitants in the investigated area. Strep-A Total is the number of tests performed expressed as % of number of visits

<table>
<thead>
<tr>
<th>Year</th>
<th>Total N</th>
<th>/1000 inh.</th>
<th>Strep-A pos</th>
<th>Strep-A neg</th>
<th>ND</th>
<th>Strep-A Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>nS (%)</td>
<td>% ab</td>
<td>nS (%)</td>
<td>% ab</td>
</tr>
<tr>
<td>2000</td>
<td>8325</td>
<td>57</td>
<td>32</td>
<td>96</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>2001</td>
<td>8353</td>
<td>57</td>
<td>35</td>
<td>95</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>2002</td>
<td>6778</td>
<td>46</td>
<td>28</td>
<td>95</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>2003</td>
<td>6785</td>
<td>46</td>
<td>32</td>
<td>90</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>2004</td>
<td>6288</td>
<td>43</td>
<td>31</td>
<td>91</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>2005</td>
<td>4875</td>
<td>33</td>
<td>18</td>
<td>92</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

In sore throat, a positive Strep-A test result was followed by antibiotic prescription in about 92% of cases and, when negative, prescription followed in 40%. The number of antibiotic prescriptions to patients with a negative result declined from 45% to 37% (2000→2005). When no test was performed, 64% received antibiotics (Table 7).
A CRP test was performed at an average of 36% of all consultations for RTI, 50% of all common cold visits, 52% of pneumonia and 48% of acute bronchitis. For patients receiving the diagnoses acute bronchitis and pneumonia, the number of CRP tests performed during the studied years remained basically unchanged (Table 8).

**Table 8. Treatment with antibiotics (% ab; bolded) related to outcome of CRP <50 or ≥ calculated for 2000-2005. ND = CRP not done. Tot CRP is number of CRP tests performed for each diagnosis. nC (%) is number of CRP tests expressed as % of number of visits calculated for positive and negative results separately and for each of the two diagnosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>nC (%)</th>
<th>% ab</th>
<th>nC (%)</th>
<th>% ab</th>
<th>% ab</th>
<th>% ab</th>
<th>% ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>2486</td>
<td>20</td>
<td>63</td>
<td>32</td>
<td>78</td>
<td>44</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>2461</td>
<td>22</td>
<td>65</td>
<td>34</td>
<td>83</td>
<td>45</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>2198</td>
<td>21</td>
<td>69</td>
<td>33</td>
<td>83</td>
<td>41</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>2007</td>
<td>20</td>
<td>65</td>
<td>31</td>
<td>80</td>
<td>38</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>1944</td>
<td>19</td>
<td>60</td>
<td>27</td>
<td>79</td>
<td>39</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>2629</td>
<td>21</td>
<td>65</td>
<td>29</td>
<td>84</td>
<td>46</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Consultations with CRP < 50 resulted in a prescription of antibiotics in about 54% and 65% of cases when the diagnosis acute bronchitis or pneumonia, respectively was given. Roughly, 9% of patients with the diagnosis acute bronchitis had CRP ≥50 and roughly 92% of these received antibiotics (Table 8).
Antibiotics were prescribed more extensively in the treatment of diagnoses indicating a bacterial etiology, irrespective of the outcome of measured CRP, in contrast to ‘viral’, where the prescription rates for antibiotics rose with higher CRP values (Figure 12).

Figure 12. Treatment with antibiotics in relation to different CRP interval as well as the type of infection. Note the “bacterial” diagnoses are treated with antibiotics independent of CRP test outcome. For “viral” diagnoses the antibiotic prescriptions rates increases with rising CRP values. ND = CRP not done
APPENDIX

**Photo 1-8.** Natural course of the healing of an eardrum after AOM with spontaneous perforation; Ear drum appearances during all follow-up visits

Eardrum appearance at inclusion; Photo 1-2

Eardrum appearance after 2-4 days; Photo 3-4
Appendix

Eardrum appearance after 7-9 days; Photo 5-6

Eardrum appearance after 3 months; Photo 7-8
ADDITIONAL UNPUBLISHED DATA

The published results in paper I were based on a randomized study of 179 children. However, we also followed a total of 82 patients who did not approve of the randomization procedure but accepted to participate in the follow-ups, after making their own treatment choice, 59 requested treatment with PcV (group 3, Table 9) and 23 did not accept use of antibiotics (group 4, table 9). The approach to accept an inclusion of non-randomized patients, but allowed to choose a treatment option, can be discussed. However, all data was analyzed separating the groups. Moreover, this strategy gave valuable information about these patients.

The median recovery time was four days in all four groups. Patients who received PcV had less pain (p<0.001) and used fewer analgesics. There were no significant differences in the number of middle ear effusion or perforations at the final control after three months. Children randomized to PcV treatment consulted less (p<0.001) during the first seven days. It was noteworthy that children with parents choosing not to give their child penicillin had similar symptom duration and pain severity at inclusion as the other children (Table 9). This could imply that these parents were better informed of the limited effects of antibiotics in AOM or had less anxiety about serious complications than other parents.
Table 9. Follow-up variables during the first week of the observation period (group)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment strategy (groups 1-4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Random to PoV (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Random to no PoV (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Own choice PoV (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Own choice no PoV (4)</td>
<td></td>
</tr>
<tr>
<td>Pain severity 2-3 (n; %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>48 (53%)</td>
<td>0.179</td>
</tr>
<tr>
<td></td>
<td>46 (58%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 (70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (52%)</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (28%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (18%)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>6 (29%)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (14%)</td>
<td>0.116</td>
</tr>
<tr>
<td>Day 3-7 (max)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Mean # days (range) with pain severity 2-3</td>
<td>0.1 (0-6)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>0.5 (0-5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3 (0-5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 (0-2)</td>
<td></td>
</tr>
<tr>
<td>Analgesics (Yes; n; %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>57 (63%)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>61 (76%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 (79%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (90%)</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>20 (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43 (54%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (35%)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>11 (62%)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>9 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (34%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (18%)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>9 (43%)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>4 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (13%)</td>
<td>0.099</td>
</tr>
<tr>
<td></td>
<td>6 (11%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (29%)</td>
<td></td>
</tr>
<tr>
<td>Day 4-7 (max)</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (10%)</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Median (range) # of doses day 1-7</td>
<td>0.0 (0-8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 (0-17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0 (0-28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 (0-12)</td>
<td>0.697</td>
</tr>
<tr>
<td>Fever&gt;38°C (n; %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>18 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (16%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (18%)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (11%)</td>
<td>0.088</td>
</tr>
<tr>
<td></td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2%)</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>Day 3-7 (max)</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Mean # days (range) of fever 1-7</td>
<td>0.7 (0-5)</td>
<td>0.867</td>
</tr>
<tr>
<td></td>
<td>0.8 (0-6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.7 (0-5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.4 (0-3)</td>
<td></td>
</tr>
</tbody>
</table>

Footnotes to table 2:

i) Group 1 differed from 2 (Fishers exact test; p=0.001)

ii) Fishers exact test between 1 and 2, the other groups not tested

iii) Group 1 differed from 2 (p=0.000), 3 (0.01) and 4 (0.001)

iv) Fishers exact tests between 1 and 2, were for Day 0 p=0.095, Day 1, p=0.001, Day 2, p=0.001, Day 3 p=0.001. The other groups not tested.

v) Group 1 differed from 2 (p=0.000), and 4 (0.001) and group 3 differed from 2 (0.010) and 4 (0.036)

vi) Only tested between groups 1 and 2 due to the small number, p=0.088 Fishers exact test.
DISCUSSION

The connecting thought in this thesis is a concern for the frequent use of antibiotics in patients with acute otitis media or other respiratory tract infections in primary health care.

The two prospective clinical investigations included in this thesis (Papers I & IV) were performed to address the management of AOM with or without perforation, questioning the necessity of antibiotics. Paper I supported the conclusion that treatment with PcV in sporadic AOM provided only minor symptomatic benefits of questionable clinical importance. In AOM with spontaneous perforation, patients were followed without immediate antibiotic treatment. The results indicated that a majority of such AOM healed without antibiotics, but that those with a prolonged healing process were patients presenting with abundant, purulent secretion, pulsating ear drum appearance and findings of *S. pyogenes* in aural secretion.

The surveys presented in papers II & III were performed to address patient consultation habits and physician management of infections in primary care over time. The results showed a decline in visiting rates by 23% between 1999 and 2006. The diagnoses AOM and sore throat declined yearly by >10%. The proportion of patients obtaining antibiotics was almost constant over the years and about 45% of all consultations for RTI resulted in antibiotic prescription, mostly PcV (60%). In sore throat, a negative outcome of Strep-A testing resulted in antibiotic prescription in 40% of visits. CRP was analyzed in 36% of consultations for RTI. In common cold and acute bronchitis antibiotic prescription rates rose with rising CRP values.
Discussion

Methodological considerations

Paper I

In paper I, the open-label randomized study design can be discussed. A double-blinded randomized trial was not possible due to the difficulty in creating a placebo mixture that could not be easily distinguished from the active substance, as PcV has such a characteristic taste and smell. Even urine gets a special penicillin smell from PcV that is easy to recognize. However, the open study design is more realistic since it follows the normal daily procedures in primary health care where both parts are aware of the chosen clinical treatment. The lack of placebo or blinding of the study may have resulted in a more careful registration of symptoms in patients without antibiotic treatment, which could overestimate the occurrence of symptoms and lead to more phone contacts or new visits. It can be argued, that blinding may have caused concern for placebo treatment with an inactive substance causing more contacts and new visits.

It seems obvious that not all GPs and Health Centers included consecutive children with AOM and the number of inclusions was substantially less than was initially intended in order to reach a desirable power (>80%) for most of the clinically important differences. After two years, the recruitment of new patients gradually declined and the study was eventually closed. One reason for this decline may have been that recommendation of antibiotic restriction was spreading in the community and that people therefore adopted a “wait and see” policy. Another reason may have been busy work schedules since the inclusion procedure was time-consuming and participation was unsalaried. Despite low recruitment rates, we found no evidence of selection bias where children included at low-including clinics had milder symptoms, shorter duration of illness or showed different course of healing according to diaries.
Papers II & III

The electronic patient record system (EPRS) is well implemented in Sweden and has been found suitable for describing consultation rates, diagnoses, performed analyses and antibiotic prescription in the healthcare system [65, 81, 117, 118]. The used EPRS database comprised more than 240,000 visits (145,000 inhabitants) for RTI (office and out-of-hours) performed in primary health care in Kalmar County during the 6½ years studied. The registration of diagnoses and prescription of all pharmaceuticals including e-prescriptions was mandatory and performed exclusively by physicians. Nurse-lead task forces were not generally adopted in Kalmar County. It was compulsory to register all performed analyses in the EPRS laboratory module.

There are some limitations in using retrospective data from an EPRS. During the studied period, patients with a sore throat could first consult a nurse in four of the participating 23 health care centers. These visits were then registered by a GP and given a diagnosis, but in two of the centers, some consultations without an antibiotic prescription might have been missed. This could slightly underestimate the total number of sore throat visits, but should not influence the changes over time, since there were no organizational changes in the division of tasks between GPs and nurses over the years. Further, it is not possible to calculate within which time frame a consultation is considered as the same or a new episode, which may influence diagnostic labeling as well. We have probably overestimated the number of cases of AOM and pneumonia and consequently underestimated the prescription rate of antibiotics, since we cannot distinguish acute visits from therapy failure and control visits. On other hand, we may have overestimated the prescription of antibiotics when prescribed according to “wait and see” policy if the patient decided not to use the prescription.

In addition, the criteria for diagnostic labeling of RTI used by different physicians may vary, and antibiotic treatment may have influenced the choice of diagnosis. Furthermore, the results of the analyses performed – CRP and Strep-A – may have influenced the choice of treatment and diagnosis.
Discussion

**Paper IV**

The direct referral of possible participants to including E.N.T clinics minimized the selection bias, although not all eligible children were enrolled (non-motivation due to necessity of several follow-up visits, need of antibiotics, transportation problems etc.). We have not evaluated possible participants who chose not to be referred but we assumed that there were no differences in the severity of illness between groups.

The major strength of this study was that inclusion and successive follow-up visits were performed by experienced otolaryngologist, which ensured maximal reliability. The follow-up visits gave opportunity to follow the macroscopic changes of the eardrum and type of secretion during the different phases of the healing process with a possibility of photographic documentation. The small number of children included limits the possibility to draw conclusions, but the study still provides information on the natural course of AOM with spontaneous perforation with special emphasis on the macroscopic changes of the eardrum and secretion over time in relation to microbiological findings.

**Management of AOM and RTIs in Primary Care**

**Acute otitis media**

Respiratory tract infections (RTIs) are one of the most common reasons for consulting primary care. AOM is one of the most common reasons for consultation during childhood. The diagnosis of AOM is clinical based upon the history and direct inspection with finding of bulging red or pale eardrum with reduced mobility or a visible perforation. About 70-80% of children will experience at least one attack during preschool years [119].

The most usual etiology is *S.pneumoniae* accounting for 30-50% of all bacterial findings, *H.influenzae* 15-30%, *M.catarrhalis* 1-9% and *S. pyogenes* 1-5% [120]. The national Swedish guideline from year 2000 recommends treatment with PcV for children with AOM below the age of 2 and over 16 years of age and for children with perforated otitis. For otherwise healthy children, 2-16 years of age, with sporadic cases of AOM (<3/6months), the Swedish guideline suggested a “wait and see” treatment alternative [119]. In addition, the
guideline also stated that if the earache spontaneously subsided within 24 hours, a physician visit was not obligatory.

In our study, the incidence of AOM decreased markedly from 2000-2005 and accounted for 24 visits/1000 inhabitants and year 2005 (Paper II). This decrease may have been the result of the new guidelines, but as illustrated in Figure 6 (Paper III), the decline occurred first after 2002. Spreading and implementing new knowledge is often difficult and time consuming, since both the profession and the public must be informed. The observed change may have been facilitated by the use of “Tele-Q”, a nurse callback advice support system. This system forced patients to contact primary care by before visiting, which gave the opportunity to prevent visiting by informed decision and adopt a “wait and see” policy in accordance with guidelines.

The proportion of registered AOM prescribed antibiotics did not change over the years. Of registered AOM, 76% were prescribed antibiotics over the years (Paper II). In reports from other countries, the prevalence of antibiotic treatment for AOM varied: 44% in Norway [121], 48% in the Netherlands [122], 80% in USA[123], Australia and New Zealand, and 81% in UK [124]. However, the definition of AOM may vary between countries, as does physician availability, which in turn may affect selection of patients consulting primary care.

The results of paper I showed that the benefit of antibiotics in treatment of AOM was evident but limited. Children treated with antibiotics were relieved from pain 0.4 days earlier and their consumption of analgesics was lower compared with those not treated with antibiotics. The prevalence of the treatment failures or of new AOM episodes or SOM after 3 months was similar. Our results were in line with most national as well international randomized placebo controlled studies and newer meta-analysis [15, 19, 22, 125, 126]. This limited positive effect must be evaluated in relation to possible negative effects of antibiotic treatment such as individual side effects and development of resistance. In addition, one recent study indicated that use of antibiotics in AOM may increase the number of recurrences [20]. Therefore, it seems justified to recommend “wait and see” for three days instead of immediate antibiotics for children with AOM.

Current opinions regarding the application of “wait and see” approaches in the management of acute otitis media in children vary across Western
countries where, among others, Scotland [127], UK [128], Germany [129], and Denmark [130], have already adopted a “wait and see” approach in children aged ≥ 6 months. The number of days of watchful waiting varies from 24 hrs. in Germany to 72 hrs. in Denmark.

The frequency of mastoiditis in children aged 0-16 was 2.6 /100.000 children according to a new, unpublished Swedish study (personal communication). According to this study, the number of cases was constant between 1993 and 2007, thus indicating that the decreasing visiting frequencies for AOM by 12% per year (Paper II) and the reduction in the prescription of antibiotics to children in Sweden did not affect the frequency of mastoiditis. This has also been noted in other studies [131-133].

AOM with perforation

According to National Swedish Guideline from year 2000, all AOM with perforation should be treated with antibiotics, preferably PcV. The frequency of spontaneously draining AOM is as high as 15% according to some studies [120]. Spontaneous perforation and otorrhea has in several reviews been suggested as a risk factor for complications, but we have not found any study specifically addressing children with AOM complicated with spontaneously ruptured tympanic membrane. The prospective investigation presented in paper IV is to our knowledge the first study observing the course of AOM with a spontaneous perforation without initial use of antibiotics. The small number of children included limits the possibility to draw definitive conclusions but the results indicated that about 80% of children presenting with perforated AOM most likely do not benefit from antibiotic treatment.

In our investigation, the macroscopic appearance of the eardrum in relation to different secretion characteristics was correlated to the clinical course. The constellation with abundant and purulent secretion in addition to pulsating tympanic membrane had acceptable sensitivity and specificity to predict absence of improvement or antibiotic prescribing at follow-up visits.
Alloicoccus otitidis; a gram positive coccus, was recovered for the first time in middle ear effusions in children in 1989 [134]. The bacterium is difficult to culture but easy to identify with PCR-techniques. Ashhurst-Smith et al. [135] found that all isolates were sensitive to penicillin and tetracycline but 70% were resistant or partially resistant to erythromycin. The clinical significance when presented in AOM has been questioned in several studies [135-138]. In our study, one of 15 patients with A.otitidis as the only bacteria in aural secretion received antibiotics.

Regarding the microbiological analyses, PCR from otorrhea was found to have 50% higher sensitivity (detection rate) (85% versus 44%) as compared to bacterial cultivation. We also found that only 20% of bacterial growth from nasopharynx was recovered in aural secretion, which implies that the use of nasopharyngeal cultivation as a guide for the choice of antibiotic may not be reliable.

All six patients with growth of S.pyogenes in the ear canal received antibiotics at the first follow-up visit since their clinical condition had not improved. This indicates that a rapid test for S.pyogenes performed on aural secretion might be one way to identify some of the patients that may benefit from early antibiotic treatment. The study indicated that watchful waiting for three days in most children with AOM and otorrhea was justified. However, in children with abundant purulent secretion or presence of S.pyogenes immediate treatment could be recommended.

Severe complications including acute mastoiditis, labyrinthitis and brain abscess are extremely rare. However, a three-year old patient with prolonged fever after inclusion and abundant purulent secretion, who also developed a contralateral perforation, presented with an acute mastoiditis at the day eight follow-up. According to study protocol instructions, antibiotics should have been prescribed at the first follow-up visit under such conditions but was not. The initial sample showed growth of S.pneumoniae (in PCR and cultivation from the ear canal). The child was treated with intravenous antibiotics and cured. But, during the following 12 months, this participant developed recurrent episodes of AOM and persistent SOM with delayed linguistic development and received grommets. It can be discussed whether the mastoid infection would have been prevented by antibiotics initiated at the first follow-up visit.
Several studies have shown that mastoiditis may develop under ongoing antibiotic treatment or may present prior to development of ear symptoms [133, 139-145]. Generally, there is no clear relationship between previous ear problems and the development of complications [142, 146-148].

**Management of RTIs in Primary Care**

There is a general lack of knowledge of indications for antibiotic prescription. In Sweden, there is no national system to follow changes in indications over time to evaluate appropriateness of antibiotic use, or implementation of guidelines. Diagnosis/prescription studies had been performed in 2000, 2002 and 2005 [9]. These studies were important but small, performed in one week and difficult to maintain over time. Therefore, there was a need for greater knowledge of indications, antibiotic prescription and use of rapid tests in primary care.

In this study, paper II, an antibiotic was prescribed in 45% of all consultations for an RTI (including AOM) during the period 1999-2005 (Table 10). The most prescribed antibiotics were PcV (60%) and doxycycline (18%). Common cold was the most common diagnosis and sore throat (tonsillitis & pharyngitis) was the most common reason for an antibiotic prescription followed by AOM (Table 10).

Visits for RTIs, including AOM, declined by 23% and the total number of antibiotic prescriptions by 33% between 1999 and 2005 (Papers II & III). Children from 0-6 years of age consulted most with an average of 905 visits/1000 inhabitants of the same age group and year and adults 18-44 years made an average 231 visits/1000 inhabitants of the same age group and year. AOM and sore throat showed declining consultation rates by approximately 10% per year, but the frequency of acute sinusitis, acute bronchitis and pneumonia was similar compared over time (Paper II & III). Declining consultation rates for RTIs has been reported from other countries but most international studies refer to data from the late 90’s to 2001 [124, 149], except Thompson et al. [150]. They looked at antibiotic prescription for children up to 18 yrs. in the UK from 1996-2006 and found a decline in the prescription of antibiotics by 24% between 1996 and 2000 but the prescription rates increased again by 10%
during 2003–2006, mostly for non-specific upper respiratory tract infection and abnormal signs and symptoms. Thompson, in agreement with our findings, found a reduction in prescriptions for AOM and tonsillitis / pharyngitis by nearly 50% during the studied years.

Table 10. Antibiotic prescriptions per visit resulting in an RTI diagnosis in primary care in Kalmar County during six complete infectious seasons 2000-2005. Data from paper III

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of visits (total)</th>
<th>Antibiotics prescribed (% of visits)</th>
<th>Prescriptions/1000 inh/and year (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold</td>
<td>73715</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>28910</td>
<td>83</td>
<td>27</td>
</tr>
<tr>
<td>AOM</td>
<td>27077</td>
<td>76</td>
<td>23</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>22160</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>18173</td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13725</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>12494</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>25300</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Totals (abs)</td>
<td>221554</td>
<td>45</td>
<td>111</td>
</tr>
</tbody>
</table>

Footnotes to table: abs = absolute values; Others = less frequent used diagnoses lumped together

Common Cold

Common cold accounted for most visits for RTI corresponding to 79/1000 visits per capita for 2005 and the number was almost constant 1999→2005 (Paper II). Common cold was the most common diagnosis in all age groups except for those older than 75 years, where pneumonia dominated. Antibiotics were prescribed for 16% of patients with the diagnosis common cold (Paper III). This may seem a small proportion, but still account for a large number of prescriptions. Though the severity of the infection cannot be evaluated in EPR-records, the number appears high. There is no study showing effect of antibiotic treatment on common cold (Cochrane) [67, 151]. However, common cold may be difficult to differentiate from a bacterial rhinosinusitis and these diagnostic groups may therefore overlap.
**Discussion**

**Acute sinusitis**

Acute sinusitis was the fifth most frequent RTI diagnosis registered in primary care in Kalmar County (Paper II)(Table 10) accounting for 21/1000 visits per capita and year in 2005. The frequency remained fairly stable as did the proportion of antibiotic prescriptions (80% of visits) over the years. A similar proportion in visiting rates was found in two other Scandinavian studies performed by André et al. [9] and Rautakorpi et al. [152]. In two Dutch studies [122, 153] and one report from the UK [154], the antibiotic prescription rates were somewhat lower than in the Scandinavian studies (67-70%).

The diagnosis of purulent maxillary sinusitis is based on obstructive symptoms and discomfort due to inflammatory edema and clinical signs. Randomized placebo-controlled studies of maxillary sinusitis, diagnosed by clinical signs alone, showed no difference between antibiotics and placebo (Cochrane) [155]. In a Norwegian study Lindbaek found that antibiotics shortened symptom duration significantly, when the diagnosis was based on radiological findings [156]. Young et al. [157] in a recent meta-analysis of individual patient data from 2547 adults in nine trials concluded that 15 patients with rhinosinusitis-like complaints need antibiotics before one additional patient benefits from treatment.

New Swedish guidelines were published in 2005, so they could not have influenced the results of our study. The guidelines concluded that antibiotics may benefit patients with prominent sinus pain, pus findings in middle meatus or nasopharynx, two-phased onset and an elevation of CRP or ESR after 10 days of symptoms [72]. Methods more precise are sinus puncture or X-Ray but these methods are often impractical in primary care.

The results presented in paper III show that CRP was performed in 15% of patients diagnosed as sinusitis and 68% of those received antibiotics at CRP <10. Antibiotic treatment of patients presenting with CRP <10 may still be in accordance with guidelines since other diagnostic criteria could not be obtained from the EPRs. But the use of CRP as a reliable diagnostic criterion may be questioned especially when the value is not elevated. Hansen [158] found, in a clinical trial of 170 patients with suspected maxillary sinusitis of which 120 participants were punctured, that a positive bacteriological culture became more common with increasing ESR and CRP, but normal ESR values
Discussion

were recorded in 42% and normal CRP values in 26% of patients with verified purulent sinusitis.

In Sweden, PcV is the recommended treatment and amoxicillin in case of treatment failure or new infection within four weeks. In our study, PcV accounting for 62% and doxycycline 22% of all antibiotics prescribed for sinusitis. It is difficult to explain the rather high prescription rate of doxycycline, but since we cannot distinguish between primary visits and revisits, the prescription of doxycycline may be a consequence of suspected treatment failure or prescribed for the treatment of concurrent pulmonary or other infection. Serious complications are rare, and I have not found any reliable data regarding the frequency of these events in comparative studies of treatment with or without antibiotics [155].

Pharyngotonsillitis (Sore throat)

The prevalence of acute sore throat was 30 visits per 1000 inhabitants and year during 2005 (Paper II) and was the second most frequent diagnosis over the studied years. The number of visits declined by almost 50% during the observed six years (Paper II), most likely a consequence of a more restrictive approach following the implementation of the new Swedish guidelines for the treatment of sore throat in 2001 [71]. The guidelines stressed that the Strep-A test should not be used if signs of viral infection exist (coughing, hoarseness, coryza), and recommend the use of Centor criteria [82, 83] to select patients who might gain from antibiotic treatment and use of Strep-A test before prescribing antibiotics. Studies have shown that antibiotics may shorten the symptom duration by 1-2½ days if the patient meets at least three Centor criteria and shows growth of S.pyogenes [159-161].

The decreasing frequencies in visiting rates and in antibiotic prescription rates for sore throat in papers II and III were observed in other Swedish counties during the same period. André et al. [9] described a reduction by 41% in the number of consultations and antibiotic prescriptions for sore throat between 2002 and 2005. In two studies from UK, Ashworth et al. and Smith et al. found declining numbers of consultations and antibiotic prescription rates for sore
Discussion

throat by almost 50% during the periods 1995–2000 and 1993–2001, respectively [124, 154, 162].

Patients who received the diagnosis sore throat were, in 65% of visits, prescribed antibiotics. PCV was the preferred drug in treatment of sore throat and prescribed to 82% of all patients receiving antibiotics. This is also the drug of choice according to the guidelines. A Strep-A test was performed in approximately 60% of visits. In our survey presented in paper III, patients diagnosed with sore throat received antibiotics in 40% of all cases, despite negative outcome of Strep-A testing, and 64% received antibiotics for sore throat without testing. This implies that the national guidelines were not properly followed. The reason for deviating from the national guidelines may have been fear of complications or diagnostic insecurity. The prevalence of acute glomerulonephritis and rheumatic fever is extremely low in Western countries today, mainly due to the fact that strains carrying virulence factors responsible for these sequelae are not circulating in the population [163, 164].

An improper use of rapid diagnostic tests to diagnose S. pyogenes may result in treatment of carriers suffering from viral conditions. The carrier rates of S. pyogenes in healthy children are high. According to Gunnarsson et al. [165] the presence of S. pyogenes in healthy pre-school children (≤ 6 yrs) in full time day care (>30 h/week) was as high as 25-29% during the winter and summer respectively.

**Acute bronchitis and pneumonia**

Acute bronchitis and Pneumonia accounted for 27 and 18/1000 inhabitants and year respectively and the number was constant over the years (Paper II) as was the proportion of patients prescribed antibiotics. Our findings were in line with another Swedish study by Andre et al [9].

Two years after data collection presented in papers II & III, new guidelines for the treatment of lower respiratory tract infections were developed in 2007 [166]. The guidelines stressed to avoid antibiotics to patients with acute bronchitis or unclear LRTI symptoms without severe general distress, high CRP values or to patients with pneumonic infiltrates on X-Ray.
In our study, patients diagnosed with pneumonia received antibiotics in only about 60% of cases but the number of cases was probably overestimated and the prescription of antibiotics underestimated, since it was impossible to distinguish between acute visits, therapy failures or control visits in the EPR-system.

Doxycycline was the most common drug for the elderly and the treatment of acute bronchitis. Approximately 60% of patients diagnosed with acute bronchitis received antibiotics (Paper III). The observed high use of doxycycline in lower RTI is not supported by current Swedish recommendations, but has been noted in prior studies [9, 117, 167]. One explanation could be that this may have arisen from concern regarding \textit{M. pneumoniae} infections. The prescription rates for pneumonia and acute bronchitis varied in other European countries. Kuyvenhoven in a Dutch and Rautacorpi in a Finnish study found higher prescription rates than in paper III presented for both pneumonia and bronchitis (73% and 69 for pneumonia and 79 and 70% for acute bronchitis, respectively, than presented in paper III for both pneumonia and bronchitis) [152, 168]. Akkerman found in another Dutch study from 2000 lower contact-based prescription rates; 26% for bronchitis and 78% for pneumonia [153].

Lower respiratory tract infections represent a source of considerable diagnostic uncertainty. To distinguish between acute bronchitis and pneumonia may be difficult [169, 170] and antibiotics are often prescribed empirically. The etiology of acute bronchitis is most often viral [171] and pneumonia bacterial where virus may coincide [170]. The bacteria most often detected in patients with suspected pneumonia and X-Ray verified chest infiltration were \textit{S.pneumoniae}, \textit{H.influenzae} and \textit{M.pneumoniae}. Holm et al. [171] found that well-defined, bacterial agents accounted for about 30% of findings in lower RTIs, airway virus 13% and in 56% of samples, no etiologic agents were detected. Lagerström [172] found, in a primary care based study of 177 patients with clinical diagnosed pneumonia X-Ray, infiltrates in 46% of patients and could obtain acceptable sputum specimens from approximately half the patients. The dominating bacterial finding was \textit{H.influenzae} while \textit{S.pneumoniae} was found to a lower extent which was unexpected but in contrast to hospital based studies [173].

Studies have indicated that high CRP values >100 during the first week of illness or values >50 during the 2nd week may indicate possible pneumonia but can also be found during the initial stages of aggressive viral infections.
Discussion

[89, 92, 174-176]. In our survey, the CRP-test was performed at an average of 52% of pneumonia and 48% of acute bronchitis visits (Paper III). Consultations with CRP <50 resulted in a prescription of antibiotics in about 54% of cases when the diagnosis acute bronchitis was made and in 65% of pneumonia cases. The extensive use of CRP and prescription of antibiotics at CRP <50 is not recommended by the 2007 guidelines. The number of antibiotic prescriptions to patients receiving the diagnosis acute bronchitis was extensive. Hopefully, the new guidelines will decrease the inappropriate use of antibiotics for acute bronchitis.

Practical implications and future research

Resistance in primary care will most probably increase over time in major pathogens, *pneumococci, staphylococci* and *E.coli* and antibiotic use is a major factor in the emergence and spread of resistant bacteria. Today, surveillance of resistance in the primary care setting is insufficient and needs improvement. More studies are needed especially in the daycare setting as well as among the elderly in community dwellings.

Effective antibiotics is needed to save lives and reduce long term complications in case of meningitis, sepsis, acute mastoiditis, pneumococcal pneumonia and acute ethmoiditis. In some infections, with high complication ratios, such as in sexually transmitted infections or lime disease, treatment with antibiotics is justified even if the number of patients to be treated in order to prevent one additional bad outcome may be high. However, most common infections in primary care are likely to resolve without treatment but antibiotics may in some cases shorten symptom duration as in acute otitis media (>2 y of age), sore throat and sinusitis. Such infections are the most common reasons for consultation and therefore a contributing factor to high prescription rates in primary care. If resistance rates continue to increase, the indications for prescribing antibiotics for these common infections may be reevaluated.

In the present investigations, the visiting frequencies for the AOM and sore throat declined by almost 50% during the observed six years. The implementation of new guidelines probably contributed to that decline but the
results from papers II and III indicated that the management of these infections could be further improved. The new guidelines for AOM from 2000 suggested a wait and see alternative to immediate antibiotic prescription. The study presented in paper I support the “wait and see” policy in children aged 2-16.

Treatment of AOM with spontaneous perforation without antibiotics has not been evaluated earlier. The data presented in paper IV indicated that an active “wait and see” policy during the first 3 days can be justified in most children with otorrhea but that antibiotic treatment should be considered for children who present with abundant purulent secretion and pulsating eardrum. We also found that all patients with presence of *S.pyogenes* received antibiotics, which implied that Strep-A test performed on aural secretion might distinguish patients that may benefit in early antibiotic treatment. The treatment of AOM with spontaneous perforation should be further evaluated in randomized studies to assure sufficient data before modification of guidelines. In addition, the use of Strep-A tests on aural secretion and skin infections as well seems to be an interesting research project since no data on sample localizations other than throats are available.

The use of antibiotics in lower respiratory tract infections can be improved. A majority of patients with acute bronchitis were prescribed antibiotics that were not in accordance with evidence-based medicine. The implementation of the new guidelines developed in 2007 will hopefully change these prescription habits.

Knowledge of indications for antibiotics and changes over time is a prerequisite for interventions targeting prescription habits of physicians and the expectations of the population. The EPR system makes it possible to retrieve important information on patient visits, diagnoses, prescription of pharmaceutics, referrals and performed tests. Such information should be made available for feedback and quality-improving efforts on a regional and national basis.

The common use and lack of consequences of near-patient testing as showed in paper III implies that the guidelines were not properly followed. A possibility would be a clinical decision support system and audits, shown to have great impact on individual practice [177]. Further, the interpretation of CRP in adults presenting with a respiratory tract infection of viral etiology has
Discussion

been described [175], but no study regarding the course of CRP in children
with viral infections has been performed in outpatient care, implying a need
for new research on this patient group.
The prescription of antibiotics for infections other than RTI in Sweden is
considerable and not sufficiently studied. Studies of consultations for skin
infections and soft tissue infections and urinary tract infections would further
contribute valuable information on antibiotic prescription in primary care.

Conclusions

• The benefit of antibiotic treatment of uncomplicated AOM in children aged
2-16 was limited. Children who received PcV had some less pain, used
fewer analgesics and consulted less, but the PcV treatment did not affect
the recovery time or complication rate (Paper I).

• A majority of children presenting with AOM complicated with
spontaneous perforation healed without antibiotics. Children with
abundant purulent othorrhea, pulsating eardrum and presence of
*S.pyogenes* in aural secretion may benefit from antibiotic treatment (Paper
IV).

• The number of visits for RTIs declined by 23% between 1999 and 2005,
mainly due to declining visiting frequencies for AOM and
pharyngotonsillitis (Paper II).

• The number of infections diagnosed as AOM and sore throat declined over
the years but the visit-related prescription rates of antibiotics remained
mainly unchanged (Paper II).

• The total number of antibiotic prescriptions decreased by 33% between
1999 and 2005. Antibiotics, mostly PcV, were prescribed to 45% of patients
with an RTI (Paper II). Doxycycline was often prescribed in treatment of
acute bronchitis (Paper III).

• Near-patient tests were used extensively, and Strep-A and CRP test results
were often used and interpreted as not being in accordance with the
guidelines (Paper III).
SAMMANFATTNING PÅ SVENSKA

(Summary in Swedish)

Öroninflammationer och andra luftvägsinfektioner hör till de vanligaste besöksdiagnoserna och de orsakar en majoritet av alla antibiotikarecept i primärvården. De flesta luftvägsinfektioner är virusorsakade och självläkande, där antibiotika inte bidrar till bättre utläkning. Hög användning av antibiotika ökar risken för att antibiotikas effekt minskar pga. att bakterier blir mindre känsliga för antibiotika (resistensutveckling). Den yttersta konsekvensen kan bli att tidigare behandlingsbara infektioner kan bli livshotande då vi kommer att sakna botmedel.

Denna avhandling är tänkt att bidra till att öka kunskapen om behandling av såväl okomplicerade som komplicerad öroninflammationer med hål på trumhinnan samt om hur primärvården handlade luftvägsinfektioner mellan 1999 och 2005.

I den första öronstudien inkluderades barn i åldrarna 2-16 år som sökte sin vårdcentral med öroninflammation. Barn som ingick i studien blev slumpvis uppdelade i grupper där den ena fick behandling med penicillin medan den andra fick självläka. Denna studie visade att båda grupperna läkte ut lika bra, dock hade barn med penicillinbehandling lite kortare värk (0,4 dagars skillnad).

I den andra öronstudien på barn i samma ålder och med hål på trumhinnan, togs barnen om hand på deltagande öronkliniker som tog bakterieprover och följde barnen med flera återbesök. Antibiotika skulle enbart sättas in om barnen vid återbesök inte förbättrats eller blivit sämre. Denna studie visade att de flesta öroninflammationer med hål på trumhinnan läker fint ut utan antibiotika. Studien visade också att barn från första besöksdagen med pulserande trumhinnan och riklig varig flytning och eventuellt förekomst av 

S.pseudogenes (halsflussbakterier) i öronsekreteret bör ha nytta av antibiotika.

I de två andra studierna inhämtades data från elektroniska patientjournaler i hela Kalmar Län på alla luftvägsinfektioner för analys av enskilda diagnoser över tid samt handlägningsrutiner i primärvården. Handläggningen av
luftvägsinfektioner och öroninflammationer jämfördes med gällande riktlinjer och med nationella och internationella data.

Totalt analyserades 240 445 patientbesök som skedde under åren 1999-2005. Förkylning, halsfluss, och öroninflammation var de tre vanligaste besöksdiagnoserna. Läkarbesöken för öroninflammationer och halsfluss hade under de analyserade 6 åren minskat med nästan hälften. Öroninflammationer behandlades i nästan 80% av fallen med antibiotika där den rekommenderade behandlingen ger möjlighet för att avstå från antibiotika till barn i åldersgruppen 2-16 år under de första tre dagarna för att se om örat läker ut utan. Antibiotika förskrevs i 45% av alla besöken för luftvägsinfektioner och denna förskrivning har inte minskat under åren. PcV (Kåvepenin®) var det antibiotikum som förskrevs mest och är den rekommenderade behandling när man väljer att behandla för misstänkta bakteriella infektioner. Däremot förskrevs Doxycyklin, ett bredare antibiotikum, till över hälften av patienter med bronkit - dessa patienter bör inte behandlas med antibiotika enligt riktlinjerna. Öroninflammationer behandlades i nästan 80% av fallen med antibiotika och hade inte minskat trots att nya svenska regler ger möjlighet för att avstå från antibiotika till barn i åldersgruppen 2-16 år under de första tre dagarna.

I diagnostiken av luftvägsinfektioner användes snabbsänka samt test för halsflussbakterier. Snabbsänkan togs vid nästan 40% av alla besöken och antibiotika förskrevs även vid lätt höjda värden vid diagnoserna bronkit och lunginflammation. Användning av snabbsänka rekommenderas enbart vid nedre luftvägsinfektioner. Halsfluss ska enligt rekommendationerna enbart behandlas när ett flertal säkra halssymptom finns och ska bekräftas med ett positivt halsprov innan förskrivning av penicillin. Men i vår analys fann vi att 40% av patienterna fick antibiotika trots att halsprovet var negativt och 60% fick behandling utan att något prov togs.
Slutsatser

• Öroninflammationer hos barn i åldrarna 2-16 år behöver i de flesta fall inte behandlas med antibiotika. Blir barnen inte bra under de följande 3 dygnen skall en läkarbedömning ske.

• De flesta öroninflammationer med hål på trumhinnan läker utan antibiotika. Antibiotika behövs troligen vid riklig varig sekretion samt förekomst av halsflussbakterier i örat.

• Besöken för öroninflammation samt halsinfektioner har minskat kraftigt men antibiotika förskrevs i oförändrat omfattning vid besöken. Resultaten tyder på att de nya behandlingsrekommendationerna har påverkat antalet besök i högre grad än doktorernas förskrivningsrutiner.

• Antibiotika förskrevs i för hög omfattning vid luftvägsinfektioner och studien ger belägg för att förskrivningen av antibiotika i primärvården kan minska.

• Snabb-sänkan och halsflusstesterna har används i stor omfattning i Kalmar Län men ofta inte enligt gällande handläggningsrekommendationer.
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