ULLA-MAIJA RAUTAKORPI

Common Infections in
Finnish Primary Health Care

■

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the main auditorium of Building B,
Medical School of the University of Tampere,
Medisiinarinkatu 3, Tampere, on March 17th, 2006, at 12 o'clock.

Helene Schjerfbeck 'Toipilas' (Convalescent) 1888. Valtion taidemuseo, Kuvataiteen keskusarkisto/Hannu Aaltonen

"If you cannot measure it, you cannot improve it"
Lord Kelvin 1824 - 1907

SUMMARY

The discovery of antibiotics in 1940s led to a dramatic change in health care. Besides saving seriously ill patients to life, antibiotics also largely made modern vaccine production and surgery possible. Undoubtedly antibiotics belong to the most remarkable discoveries of medical history.

With the increasing use of antibiotics the emerging bacterial resistance to these drugs has become a problem. In earlier years the solution was to develop new antimicrobials. During the past ten years, however it has become increasingly difficult and expensive to do so and new antimicrobials with a totally new mode of action are not in sight in the near future. Therefore, it has become more important than ever to preserve the effect of the existing antimicrobials for as long as possible.

Most antibiotics are prescribed in outpatient care. Studies have shown that there are weaknesses in the diagnostics of many of the common infections in primary health care, and that the benefit of antibiotics is often only marginal in them. To be able to supervise rational antibiotic use and to focus it on those, who benefit the most from it, it is necessary to know which of those infections are or are not treated with antibiotics in Finnish primary health care.

This thesis has examined how common infections were diagnosed and treated in Finnish primary health care centres, how in line the practises were with treatment guidelines, and whether they could be directed closer towards recommendations by means of educational intervention at the work site. The data-collection method was first tested in the 20 health centres in the region of Pirkanmaa in a one-week survey in November 1994. Later, national data was collected in 30 MIKSTRA study health centres around the country during the one week (week 46) in November annually from 1998 to 2002 and in 20 control health centres in 2002.

National evidence-based treatment guidelines were drawn-up in co-operation with the Current Care Programme of the Finnish Medical Association Duodecim in 1999–2000 on the six most common infections in primary care, otitis media, sinusitis, tonsillitis, acute bronchitis, urinary tract infections and bacterial skin infections. The guidelines were implemented in study health centres by means of an interactive education at the work site, facilitated by a trained, local trainer and supported by feedback on previous data collections and patient and population information.

Respiratory tract infections comprised three quarters of all infections with common cold, otitis media and sinusitis as the most common diagnoses. Almost two thirds of patients were prescribed antibiotics in Pirkanmaa in 1994, while

little less than half received them according to the national study in 1998-2002. Patients with the common cold were rather seldom prescribed antibiotics (9–15%), while most patients with otitis media, sinusitis and urinary tract infections (82–95%) received them. Antibiotics were also prescribed to a substantial proportion of patients with acute bronchitis (59–83%), although scientific evidence does not support its benefit in that disease.

When antibiotic prescribing for respiratory tract infections was assessed as a whole, it was found out that about half of the treatments were totally or almost in line with the recommendations. One fifth of antibiotics were prescribed for infections for which they are not recommended, mainly for acute bronchitis, both before and after the intervention. In another fifth of cases, other than a first-line drug was selected without any justification being given. Prescribing in line with the recommendations in all aspects, i.e. first-line antibiotic or justified second-line antibiotic for a recommended period for otitis media, sinusitis or tonsillitis, increased from 20.6% in 1998 to 27.0% in 2001 (p<0.001).

The proportion of use of the recommended first-line antibiotics increased significantly in sinusitis, acute bronchitis and urinary tract infections during the intervention. Macrolide antibiotics, which are recommended as the second or third line drug for common respiratory tract infections, were however commonly used as first-line drugs for upper respiratory tract infections and acute bronchitis.

The proportion of antibiotic treatments with a recommended, shorter duration of treatment also increased significantly in otitis media, sinusitis and urinary tract infections during the intervention. However, in half of the cases the treatment regimen for otitis media was still longer than five days.

Of the diagnostic tools, ultrasound device was widely available and adequately used in diagnosing sinusitis (74%), but throat swab was slightly underused in throat infections (culture 37%, antigen detection 24%), although its use increased during the intervention (culture to 42%, antigen to 30%). Tympanometry was recommended for use in diagnosing otitis media, but the device was available in only a third of MIKSTRA health centres and, even if it was present, it was very seldom used (1%). No change was seen over the years, either in the number of tympanometries or in the frequency of its use. In acute bronchitis, the scant use of recommended C-reactive protein (8%) increased slightly (to 11 %).

The study revealed that although diagnostic and treatment practices were, in some aspects, well in line with the guidelines, there was quite a lot of room for improvement in other aspects. Medical education at the work site proved problematic as half of the doctors changed during the five study years. Obtained, detailed information on the diagnostic and treatment practises make it possible, however, to give precise advice on how to further improve the performance. The means are – in theory – rather simple: use of appropriate diagnostic tools, shorter courses, the use of second-line drugs only when a special justification exists, and a watchful waiting in milder cases. But to change accustomed habits needs time, education, and the motivating of professionals and patients as well as further follow-up and feedback.

6

TIIVISTELMÄ

Antibioottien eli mikrobilääkkeiden keksiminen 40-luvulla mullisti sairaanhoidon perusteellisesti. Mikrobilääkkeet ovat pelastaneet vaikeasti sairaita infektiopotilaita elämään, ja ne ovat myös suurelta osin mahdollistaneet nykyaikaisen kirurgian sekä rokotteiden valmistamisen. Mikrobilääkkeet kuuluvat epäilemättä aikamme merkittävimpien keksintöjen joukkoon.

Ongelmaksi mikrobilääkkeiden käytössä on kuitenkin muodostunut bakteerien vastustuskyvyn kasvu. Aiemmin ongelma ratkaistiin kehittämällä uusia mikrobilääkkeitä, mutta viimeksi kuluneen kymmenen vuoden aikana uusien lääkkeiden kehittäminen on käynyt vaikeammaksi ja kalliimmaksi eikä vaikutustavaltaan täysin uusia mikrobilääkkeitä ole lähivuosina näköpiirissä. Siksi on entistä tärkeämpää säilyttää nykyisten mikrobilääkkeiden teho mahdollisimman pitkään.

Valtaosa mikrobilääkkeistä käytetään avohoidossa. Infektioiden diagnostiikassa on kuitenkin havaittu olevan puutteita, ja monissa tavallisissa infektioissa antibiooteista saatava hyöty on osoittautunut vain vähäiseksi. Jotta antibioottien käyttöä voidaan ohjata kohdentumaan niitä tarvitseviin ja niistä hyötyviin on tiedettävä mihin infektioihin antibiootit suomalaisessa perusterveydenhuollossa tarkalleen ottaen käytetään.

Tässä väitöskirjatutkimuksessa selvitettiin miten tavallisia infektioita tutkitaan ja hoidetaan perusterveydenhuollossa, miten hyvin toimintatavat vastaavat hoitosuosituksia ja voidaanko hoitokäytäntöjä muuttaa työpaikalla tapahtuvan täydennyskoulutuksen avulla. Tiedonkeruumenetelmä testattiin ensin Pirkanmaan sairaanhoitopiirin 20 terveyskeskuksessa marraskuussa 1994. Sen jälkeen kansallista tietoa kerättiin 30 eri puolilla maata sijaitsevassa terveyskeskuksessa vuosittain yhden viikon ajan marraskuussa vuosina 1998–2002, sekä 20 kontrolliterveyskeskuksessa vuonna 2002.

Kansalliset, näyttöön perustuvat hoitosuositukset laadittiin Suomalainen Lääkäriseura Duodecimin Käypä hoito -ohjelmassa. Kuuden avohoidon tavallisimman infektion, välikorva-, poskiontelo-, nielu-, keuhkoputki- ja virtsatietulehduksen sekä ihoinfektioiden hoitosuositukset julkaistiin syksyllä 1999 ja keväällä 2000. Hoitosuosituksia vietiin käytäntöön tutkimusterveyskeskuksissa paikallisen kouluttajan vetämänä interaktiivisena täydennyskoulutuksena. Tätä tuettiin aikaisempiin tiedonkeruihin perustuvalla palautteella, koulutusmateriaalilla ja potilaille ja väestölle suunnatulla tiedotuksella.

Tutkimuksessa hengitystieinfektiot muodostivat kolme neljäsosaa kaikista avohoidon infektioista. Yleisimmät diagnoosit olivat nuhakuume, välikorvatulehdus ja poskiontelotulehdus. Tutkimuksen alkaessa Pirkanmaalla vuonna 1994 lähes kaksi kolmasosaa infektiopotilaista sai mikrobilääkereseptin kun tutkimusterveyskeskuksissa

7

vuosian 1998–2002 lääkettä sai vajaa puolet potilaista. Nuhakuumepotilaille määrättiin melko harvoin antibioottia (9–15%), kun sen sijaan välikorva-, poskiontelo- ja virtsatietulehdus-potilaista suurin osa (82–95%) sai reseptin. Myös keuhkoputki-tulehduspotilaita hoidettiin huomattavan usein antibiootilla (59–83%), vaikka tutkimustiedon mukaan siitä on harvoin hyötyä.

Noin puolet hengitystieinfektioiden hoitoon määrätyistä antibioottihoidoista oli täysin tai lähes hoitosuosituksen mukaista. Viidesosa antibiooteista määrättiin sellaisiin infektioihin, joihin ei antibioottihoitoa suositella, yleensä keuhkoputkitulehdukseen. Toinen viidennes määrättiin hyväksyttävään infektioon (välikorva-, poskiontelo- tai nielurisatulehdus), mutta lääkevalinta oli muu kuin ensisijaisesti suositeltu valmiste ilman, että valintaa oli perusteltu. Täysin hoitosuosituksen mukaan toteutettujen hoitojen (ts. suosituksen mukainen ensisijaislääke tai perusteltu toissijainen lääkevalinta suosituksen mukaisen ajan hyväksyttävään infektioon) osuus lisääntyi 20.6 %:sta vuonna 1998 27.0 %:iin vuonna 2001 (p<0.001). Lopuissa tapauksista infektio ja lääkevalinta olivat oikein, mutta hoito kesti turhan pitkään.

Ensisijaisesti suositeltujen lääkevalintojen osuus lisääntyi merkitsevästi sivuontelo-, keuhkoputki- ja virtsatietulehduspotilailla. Kuitenkin makrolidi-antibiootteja, joita suositellaan vasta toissijaisina lääkkeinä kaikissa tavallisissa hengitystieinfektioissa, käytettiin usein ylempien hengitysteiden infektioiden ja keuhkoputkitulehduksen ensisijaisena hoitona. Myös suositusten mukaisten, lyhyempien antibioottihoitojen osuus lisääntyi merkitsevästi välikorva-, poskiontelo- ja virtsatietulehduksissa. Seurannan lopulla puolet välikorvatulehdukseen määrätyistä lääkekuureista oli kuitenkin edelleen pidempiä kuin viiden päivän mittaisia.

Sinus-ultraäänilaite oli useimmissa terveyskeskuksissa ja sitä käytettiin sivuontelotulehdusten diagnostiikassa usein (74 % tapauksista), kun nielutulehduksen diagnostiikassa sen sijaan nielunäytteitä otettiin turhan harvoin (viljely 37 %, pikatesti 24 % tapauksista). Nielunäytteiden käyttö lisääntyi jonkin verran seuranta-aikana (viljely 40 %:iin, pikatesti 30 %:iin). Välikorvatulehduksen hoitosuositus suosittelee tympanometrin käyttöä diagnostiikan apuna. Näitä laitteita oli vain kolmasosassa terveyskeskuksia, ja niitä käytettiin hyvin vähän sielläkin missä laite oli saatavilla (1 %). Laitteiden määrässä tai niiden käytössä ei tapahtunut muutosta seurannan aikana. Keuhkoputkitulehduksessa suositeltua C-reaktiivisen proteiinin määritystä verestä tehtiin harvoin (8 % tapauksista) ja sen käyttö lisääntyi vain hieman (11 %:iin).

Tutkimuksessa havaittiin, että vaikka infektiopotilaiden tutkimus- ja hoitokäytännöt ovat joiltain osin melko hyvin linjassa hoitosuositusten kanssa, joissakin suhteissa on vielä paljonkin korjattavaa. Työpaikalla tapahtuva täydennyskoulutus osoittautui ongelmalliseksi, koska puolet lääkäreistä vaihtui viiden vuoden seuranta-aikana, mikä todennäköisesti heikensi koulutuksen vaikutusta. Tutkimuksen antaman yksityiskohtaisen tiedon perusteella voidaan jatkossa antaa kohdennettuja ohjeita hoidon laadun parantamiseksi. Keinot ovat teoriassa yksinkertaisia: diagnoosin varmistaminen asianmukaisin apuvälinein, hoitoaikojen lyhentäminen, toissijaisesti suositeltujen lääkevalintojen käyttö vain silloin kun siihen on olemassa erityinen perustelu ja seuranta ilman lääkitystä silloin kun oireet ovat lievät. Mutta totuttujen käytäntöjen muuttaminen ei tapahdu kädenkäänteessä. Se vaatii aikaa, sekä hoitohenkilökunnan että potilaiden koulutusta ja rohkaisua sekä käytäntöjen jatkuvaa seurantaa ja palautetta niistä.

8

TABLE OF CONTENTS

LIST OF ORIGINAL PAPERS

This thesis is based on the following original articles, which are referred to in the text by Roman numerals (I to IV), on some so far unpublished results and on results partly published in Finnish Medical Journal in Finnish or in congress abstracts.

   I Rautakorpi U-M, Lumio J, Huovinen P, Klaukka T. Indication-based use of antimicrobials in Finnish primary care. Description of a method for data collection and results from its application. Scandinavian Journal of Primary Health Care 1999;17:93-99.

  II Rautakorpi U-M, Klaukka T, Honkanen P, Mäkelä M, Nikkarinen T, Palva E, Roine R, Sarkkinen H, and Huovinen P on behalf of the MIKSTRA Collaborative Study Group. Antibiotic use by indication; a basis for active antibiotic policy in the community. Scandinavian Journal of Infectious Diseases 2001;33:920-26.

 III Honkanen P, Rautakorpi U-M, Huovinen P, Klaukka T, Palva E, Roine R, Sarkkinen H, Varonen H, Mäkelä M, and the MIKSTRA Collaborative Study Group. Diagnostic tools in respiratory tract infections: use and comparison to Finnish guidelines. Scandinavian Journal of Infectious Diseases 2002;34:827-830

 IV Rautakorpi U-M, Huikko S, Honkanen P, Klaukka T, Mäkelä M, Palva E, Roine R, Sarkkinen H, Varonen H and Huovinen P for the MIKSTRA Collaborative Study Group. MIKSTRA Program - a five year follow-up of infection-specific antibiotic use in primary health care; effect of implementation of treatment guidelines. Clinical Infectious Diseases 2006 (in press)

ABBREVIATIONS

AD	Academic Detailing
ATC	Anatomical Therapeutic Chemical classification
CC	Current Care (Käypä hoito)
CDC	Centers for Disease Control and Prevention
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
DDD	Defined Daily Dose
EARSS	European Antibiotic Resistance Surveillance System
ECDC	European Centre for Disease Prevention and Control
ESAC	European Surveillance of Antimicrobial Consumption
EU	European Union
FinOHTA	Finnish Office for Health Technology Assessment
FiRe	Finnish Study Group for Antimicrobial resistance
GLIMMIX	General Linear Model for Mixture Distributions
GP	General Practitioner
HC	Health Centre
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
IMS	International Medical Statistics
LRTI	Lower Respiratory Tract Infection
MIKSTRA	Mikrobilääkehoidon Strategiat–Antimicrobial Treatment Strategies
MRSA	Methicillin Resistant Staphylococcus Aureus
NBH	National Board of Health–Lääkintöhallitus
NHS	National Health Service (Great Britain)
NOMESCO	Nordic Medico-Statistical Committee
PBL	Problem Based Learning
RSV	Respiratory Cyncytial Virus
RTI	Respiratory Tract Infection
STAKES	Sosiaali ja terveys alan tutkimus ja kehittämiskeskus–National Research and Development Centre for Welfare and Health
STD	Sexually Transmitted Disease
URTI	Upper Respiratory Tract Infection
USA	United States of America
USD	United States Dollar
UTI	Urinary Tract Infection
WHO	World Health Organization

INTRODUCTION

Infections have been a major burden of mankind throughout history. A hundred years ago infections caused half of all deaths. They have had dramatic influence on the history of nations. Large pandemics have destroyed nations. It has been estimated that 'black death' (plague) killed from one third to half of the population of Europe in 1346–1453. 'Spanish Flue' (influenza-A) with its bacterial complications caused some 30 million deaths around the world in 1918–1920. Napoleon's 'La Grande Armée' was probably beaten as much by louse-born-typhus than by the Russian army (Cartwright & Biddiss, 2000) and good preventive measures against this disease in the Finnish army in the Second World War substantially improved its ability to defend our independence (Peltola, 2003b). In days of war and after large disasters like earthquakes, flood or hurricane the threat of large epidemics of cholera, diarrhoea and respiratory tract infections are taken seriously still today (Centers for Disease Control and Prevention, 2005).

Antibiotics are in many sense one of the most revolutionary discoveries in the medical history. It has been estimated, that antibiotics have raised peoples' life expectancy by 10 years (Donowitz & Mandell, 1988). As late as the 1920s, 80% of hospital patients suffered from an infection, in the 1980s only 15% (McDermot, 1982). Antibiotics made it possible to actually cure infections. They have also largely made modern vaccine production and surgery possible. In the first decades of the antibiotic era, many people began to think that infections are beaten. It is true that, thanks to vaccinations, many communicable diseases have almost or totally disappeared and many others are well controlled by improved hygiene. But antibiotics are still life-saving drugs in many situations and extremely important for mankind and therefore it is important how they are used.

It is only natural that bacteria as living organisms try to develop mechanisms to combat antimicrobials, i.e. develop resistance to them – it's simply the struggle for survival. The first successful attempt to treat a patient with penicillin, although ending in the patients' death due to insufficient amounts of the drug, was accomplished in February 1941. It was followed by an era of discoveries, generous use and disappointment. Within a few years, penicillin resistant strains of staphylococci appeared and spread to hospitals and then rapidly to the community - just as methicillin resistant staphylococci (MRSA) are doing today (Witte et al., 2004). Until recently, a new drug has always appeared just in time to circumvent the latest resistance mechanisms. This has changed, however, during the past 10–15 years. Along with the growing difficulty and increasing costs of developing new antibiotics, only a few novel antimicrobial drugs are

being developed today, as the market system forces the pharmaceutical industry to invest to the development of other drugs with safer and larger expected profit (Cohen, 1992, Norrby et al., 2005). This development forces us to seek for other means by which to control the spread of bacterial resistance.

Bacterial resistance to antimicrobial agents is today seen as a major public health threat world-wide (Wise et al., 1998). Although the World Health Organization (WHO) published it's first report on antimicrobial resistance as early as in 1983 (WHO Scientific Working Group, 1983), calls for an antibiotic policy have emerged around the Western world during the 1990s leading to statements and action plans on international and national levels. In 1998 the European Union (EU) arranged a large conference, 'The Microbial Threat', to outline a European strategy: 'The Copenhagen Recommendation' (European Union Conference 'The Microbial Threat', 1998). More recently in 2001, the World Health Organization published the 'WHO Global Strategy for Containment of Antimicrobial Resistance' (WHO, 2001). According to these statements, the means for combating the spread of bacterial resistance include reducing the disease burden and the spread of infections, enforcing surveillance, regulations and legislation related to bacterial resistance and antimicrobial consumption, improving the use of antimicrobials and encouraging the development of new drugs and vaccines.

In Finland different people, alert to the issue, came together in the mid-1990s to begin planning actions at a national level. It was soon found that even though we had good statistics on the consumption of different antibiotic compounds, information was lacking on detailed infection-specific use, which was essential to be able to give precise recommendations for improvement. As more than 80% of the total human consumption of antibiotics took place in outpatient care, the need of infection-specific information was most urgent there.

The aim of this study was first to test the methodological feasibility of a survey to map the infection-specific prescribing of antibiotics in primary health care and to get a complete picture of the distribution and management of infections and use of antibiotics. Further the study evaluated the impact to prescribing practice of implementing treatment recommendations by means of continuing medical education at the work site facilitated by trained local general practitioners (GPs). The method was piloted in a one-week survey within 20 health centres in the region of Pirkanmaa. A five-year study involving a network of 30 health centres scattered around the country explored changes in antibiotic use after the implementation of the new treatment guidelines.

14

REVIEW OF THE LITERATURE

When examining causes of death today, coded by International Classification of Diseases (ICD), infections seem to a have minor role. However, this is not the whole truth. In the case of infections, the ICD-classification is misleading as most infections, including such important causes of death as pneumonia, meningitis or influenza, are embedded in organ specific diagnoses. In 1998, 49 237 people died in Finland. Of them 363 (0.7%) died of communicable or parasitic disease, 12 822 (26%) of myocardial infarct and 10 503 (21%) of cancer. If all infections that are hidden in organ specific classes are calculated, the actual total amount of deaths caused by infections rises to some 10 000, to the same level as all deaths for cancer and, one fifth of all causes of death (Peltola, 2003a). Most obviously, infections are certainly not beaten and antibiotics are still needed as life saving drugs.

Community acquired infections

Epidemiology

Most community-acquired infections are, fortunately, not fatal but in many cases fairly mild and often self-limiting. The epidemiology of infections as a cause for general practice consultations has not been studied significantly in Finland. Most epidemiological studies on infections have focused on the incidence or prevalence of individual infections or causative agents and the whole picture of the impact of infections for society, primary health care services and antibiotic consumption in the community has remained fuzzy.

Infections as causes of consultation in primary care

Hemminki et al. made a one-day survey of 47 community general practitioners in early spring 1971 and found that infections comprised about one third of all 1511 consultations recorded (Hemminki et al., 1974). In a study by Takala and colleagues, all consultations were recording in three rural communities for six months in 1969–70, involving a total of 9900 patients (Takala et al., 1977b). The

results showed that upper respiratory tract infection was the most common diagnosis, comprising about ten per cent of all causes of consultation. A one-year survey of all consultations in a medium-sized health centre of Tammisaari district in 1979 (about 14 000 inhabitants) revealed, that out of the ten most common diagnoses, five were infections (Hagman, 1981). Acute respiratory tract infection was the second most common diagnose after hypertension, while otitis media, acute bronchitis, acute sinusitis and acute tonsillitis occupied positions four to seven. According to the Finnish Health Care Survey 1995/96, only 0.8% of visits to doctors were caused by a disease classified as 'infectious diseases', but at the same time 21% were caused by 'respiratory disorders', among which more than half (13% of all visits) were infections (Arinen et al., 1998). Figures were even higher for children: 35% 'respiratory disorders' among which 20% infections and 31% 'neurological and sensory disorders' including 28% otitis media.

In two more recent studies on reasons for general practice consultation in Finland the overview of the impact of infections to ambulatory health care remains unclear because they have used main class of ICD- and ICPC (International Classification of Primary Care)-classifications (Mäntyselkä et al., 2003, Pärnänen et al., 2001). In the latest updates of these classifications, infections are embedded in 10–12 different, organ-specific main classes among all other conditions of these organs (detailed list in Appendixes/Table 1). Thus these main classes are obviously most unsuitable for studying the impact of infections in health care as a whole.

A number of studies have examined infections in the employed population. The three most common diagnoses made by general practitioners in Finland for patients of employed aged are sinusitis, tension neck and unspecified acute respiratory tract infection (URTI) (Kokko, 1988). In a postal survey of persons aged 25–64 years in the county of Kuopio in 1992, patients reported on average 1.5 infections and 0.5 medical consultations each per year (Pirhonen et al., 1994). Young age, high education, and female gender were related to higher numbers of infections, medical attendance and days on sick leave. In mid-1970s 28% of all episodes of sick leave, and 16% of all days on sick leave were related to diseases of respiratory tract (Nyman & Raitasalo, 1978), of which more than half were probably infections (Arinen et al., 1998). It has been estimated, that over three million work days are lost annually in Finland because of infections (Reinikainen et al., 1988).

In the USA costs of viral respiratory tract infections are estimated to be some 39.3 billion US dollars annually, about the same as hypertension (40.4 billion USD) and stroke (45.4 USD) (Fendrick et al., 2003). Most of the costs arose from the cost of sick leave and re-consultations, while medication comprises some ten per cent (Birnbaum et al., 2002, Fendrick et al., 2003, Jussila et al., 2005). Although common infections are mostly not serious they have a remarkable impact on public health and the national economy in the form of lost work capacity and medical costs.

16

In Finland in the early 1970s, all infections together comprised 34% of all out-of-hour consultations (Takala et al., 1977a),with acute upper respiratory tract infections as the leading cause followed by wounds and tonsillitis. Interestingly acute otitis media was only in seventh place at three per cent. In a survey of causes of out-of-hour consultations in the Kuopio district in May 2002, the three most common causes for consultation were fever, wound and earache and the two most common diagnoses made were unspecified URTI and otitis media (Mäntyselkä et al., 2003).

Two Finnish studies from November–December 1992 and 2002 have examined causes of referrals from primary to secondary care. In the earlier study, 30% and 25% of problems leading to referral for patients aged under 15 and 15 years and over, respectively, were infection related (Vehviläinen et al., 1997). In 2002, among causes of referral, for all patients and those aged 60 and over, only pneumonia, appendicitis and fever of unknown origin reach the top 15, comprising 5,6% and 1,7% of all causes for referrals, respectively (Vehviläinen et al., 2005).

In an Icelandic multi-centre study from 1988, four out of ten of the most common diagnoses in family practice were infections: acute unspecified URTI (2.9%), acute otitis media (1.8%), bronchitis (1.7%) and unknown viral infection (1.6%), altogether 8% of all causes and 38% of the ten most common causes (Njalsson et al., 1996).

In a study made in the USA, based on the National Ambulatory Medical Survey, Armstrong et al. examined the epidemiology and trends of visits in outpatient care for infections (Armstrong & Pinner, 1999). The data were gathered as a random sample of patient visits during a randomly selected week to a sample of doctors chosen from non-federally employed physicians in the American Medical Association and American Osteopathic Association, excluding specialities of anaesthesiology, pathology, and radiology. In this study infectious diseases accounted for 19% of visits to physicians. The visit rate was highest in 0–4-year-olds and higher in females than in males. URTIs comprised 38% of all consultations for infections, followed by otitis media (15%) and lower respiratory tract infections (LRTI) (14%). The age-adjusted visit rate for infections increased from 462/1000 persons in 1980 to 575/1000 persons in 1990, but had declined again in 1996 to 483/1000 persons.

Incidence of infections in population

In the large national survey Health 2000, co-ordinated by the National Public Health Institute, a nationally representative sample of about 7000 adults aged 30 or over was interviewed in 2000–2001 regarding their health and functional capacity. Of all those interviewed 19% had suffered from a respiratory tract infection during the previous two months and some 10% had had acute diarrhoea during the previous two weeks (Aromaa & Koskinen, 2002). Respiratory tract infections were somewhat more common among the female and higher-educated

population. Almost 40% of patients having had respiratory tract infection had needed medical attention and some 2% had been hospitalized. Only 8% of those with acute diarrhoea had needed medical attention.

In the USA, the Centers for Disease Control and Prevention (CDC) perform a multistage probability sample survey annually, conducted by interviewers of the National Center for Health Statistics. In such survey 24 000 households and 63 000 noninstitutionalized people were interviewed in the USA in 1996 regarding infectious diseases (Adams et al., 1999). According to this data, there were 163.5 acute conditions per 100 persons per year in the USA of which infections comprised together some 101 (62%). The number of acute respiratory conditions was 78.9 per 100 persons, of which the number of infections was 77.3 (98%) (Table 1). According to this survey, US citizens had on average three restricted-activity days per infection per year, 1.1 work-loss days per employed working-aged person and two school-loss days per school-aged child (5–17 years of age) per year because of acute infections. In 36–99% of cases, depending on the type of infection, the condition needed some kind of medical attention.

Extrapolating these US figures to Finland, there would be about 5.3 million episodes of community acquired common infections in Finland annually. These would result in some 3 million consultations within health care, 2.5 million working days lost and 1.5 million school days lost annually. Even higher estimations have been presented earlier, however, both from Finland (Pirhonen et al., 1994) and other countries (Fox et al., 1972, Monto, 1994, Monto & Sullivan, 1993, Monto & Ullman, 1974).

Aetiology

Infections of the respiratory tract have a seasonal variation that follows the seasonal fluctuation of epidemics of respiratory viruses. In temperate areas, respiratory illness rates are highest during the cold season, while in the tropics during the rainy season. Individual respiratory viruses have slightly different seasonal patterns. Rhinovirus outbreaks, for instance, occur typically in the early autumn and mid to late spring, while coronaviruses are most common during the winter months (Gwaltney Jr, 2005b). These, and most of the other common respiratory viruses, are not registered in the Finnish Infectious diseases register. The epidemic peak of influenza-A -virus is typically in December/January in Finland, while the Respiratory Syncytial (RS) -virus has typically two peaks, a lower one in late spring and a higher one in mid winter (Figure 1). Secondary bacterial infections of the respiratory tract as well as the use of antibiotics follow the seasonal fluctuation of respiratory viruses (Talbot et al., 2005) (Figure 2).

Table 1. Incidence of acute conditions caused by infections/100 persons/year and the burden to society based on Centers for Disease Control and Prevention (CDC) National Health Interview Survey, USA 1996

Type of acute condition	No. of acute conditions /100pers/year	Per cent medically attended	No. of restricted-activity days /100pers/year	No. of work-loss days/100 employed/y	No. of school-loss days/100 youths 5–17/y
Common cold	23.6	43.0	56.0	15.6	41.5
Influenza	36.0	36.3	131.1	55.6	74.4
Other acute URTI*	11.3	87.0	31.1	13.4	22.7
Acute bronchitis	4.6	90.7	23.4	9.2	6.2**
Pneumonia	1.8	89.8	20.7	2.0**	5.2**
RTI*** total	77.3		262.3	95.8	150.0
Acute ear infections	8.2	98.6	16.6	2.7**	10.1**
Intestinal virus	6.0	36.3	14.2	5.3**	15.9**
Viral infections, unspecified	5.7	67.1	17.7	4.3**	16.7**
Acute urinary conditions**** (50% of total)	1.6	99.4	2.2	1.1**	0.1**
Acute skin conditions**** (50% of total)	0.95	88.8	2,5	0.5**	1.7**
Fever, unspecified	1.8	57.2	4.7	0.9**	4.5**
All infections, total	101.6	55,5	320.2	110.6	199.0
All acute conditions (% infections)	163.5 (62)	67.9	624.0 (51)	284.0 (39)	296.9 (67)

*URTI = Upper Respiratory Tract Infection

**Figure does not meet standard of reliability or precision set by CDC report

***RTI= Respiratory Tract Infection

****50% infection related, own estimation

Figure 1. *Cases of Influenza-A and RS-viruses notified to the Infectious diseases register by month in 1997–2003. Unfilled dots imply to November when data-collections of MIKSTRA study took place. (Source: http://www3.ktl.fi/stat/)*
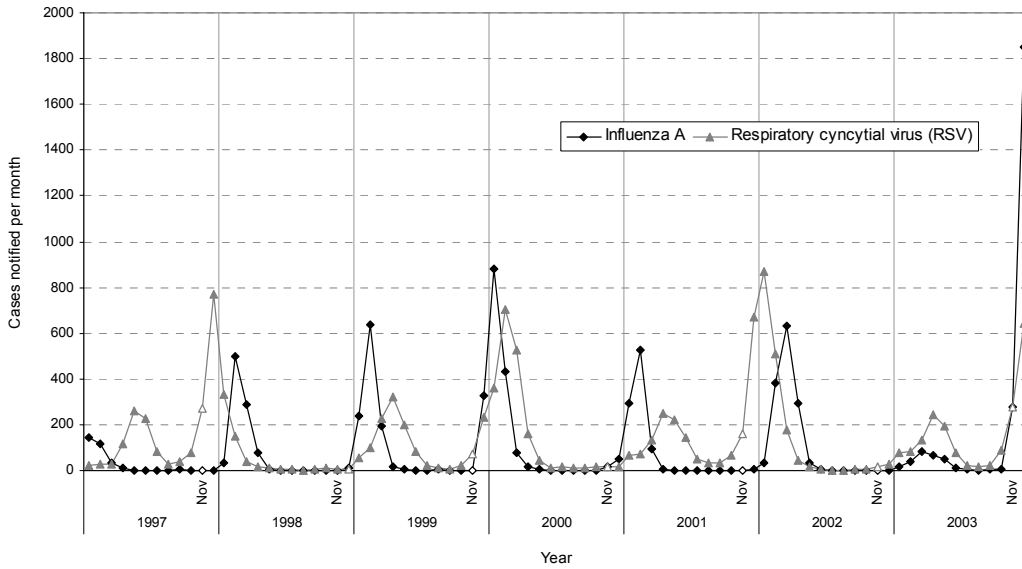
Figure 2. *Prescriptions of antimicrobials (J01) per month in Social Insurance Institute's prescription register years 1998–2002 (dots for November filled)*

20
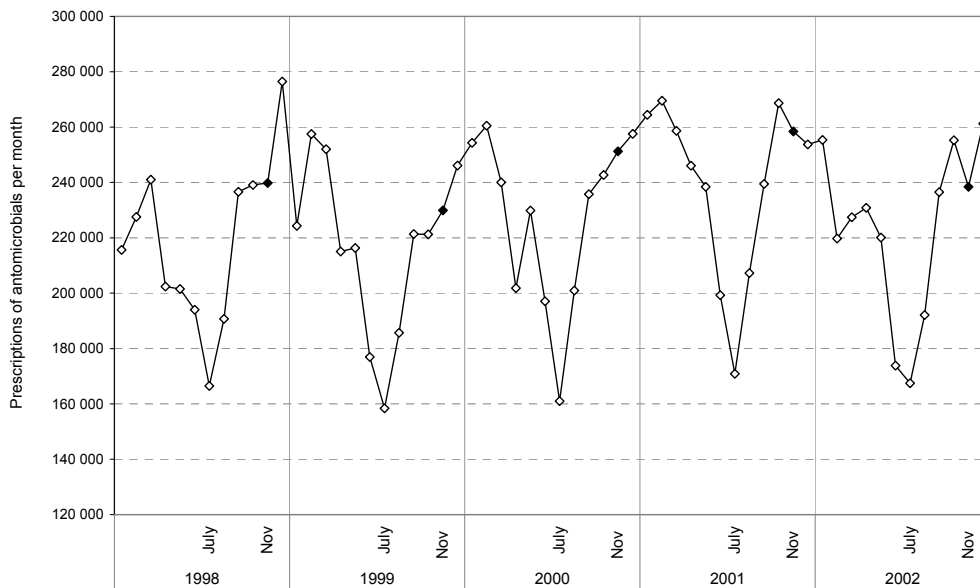
The most common of all infections is unspecified viral upper respiratory tract infection (URTI) or common cold. Rather than being an independent disease, the common cold is "a group of diseases caused by several viruses manifesting themselves with a variety of symptoms of the respiratory tract" (Gwaltney Jr, 2005b). Quite often the paranasal sinuses, middle ear and tracheobronchial tree are also involved, but only a small proportion of these inflammations are complicated by bacterial infections.

The most common viruses causing unspecified URTI are presented in Table 2. Within each of the virus groups there are several antigenic types so that there are approximately 200 different viruses causing a common cold that have been identified to date. Rhinoviruses are responsible for up to half of all cases with varying severity (Mäkelä et al., 1998, Monto & Sullivan, 1993, Pitkäranta & Hayden, 1998). Similarly, a limited number of bacteria are mainly responsible for bacterial complications of viral respiratory tract infections (Table 3), although there is wide variety of additional, less common causative agents. As symptoms and signs are in most cases quite similar irrespective of whether the causative agent is a virus or bacteria, the challenging task for the physician is to distinguish those patients who are in need of and can benefit from antibiotic therapy.

Pharyngeal symptoms are involved in most viral upper respiratory tract infections. In practice, however, the main task in primary care is to identify those patients having a group A streptococcal tonsillitis (sometimes in epidemics also group C and G) as other bacterial causative agents are rare (Bisno et al., 2002, WHO Model Prescribing Information, 2001). The absolute benefits of antibiotic treatment in acute throat infections are modest. Antibiotics shorten the illness by an average of about one day, but the benefit is increased in people with streptococci growing in the throat (Del Mar et al., 2004). Antibiotics also reduce the risk of rheumatic fever in communities where this complication is common, but the incidence of this complication in Western countries is extremely low. The Finnish treatment guideline for throat infections recommends antibiotic treatment in case of a positive throat swab -test for group A streptococci or, in case of epidemics, to group C or G (Sarkkinen et al., 1999).

Even 90% of patients with acute URTI have symptoms of rhinosinusitis (Berg et al., 1986, Gwaltney Jr, 1994) and up to 39% of adults (Puhakka et al., 1998) and 88% of children (Kristo et al., 2003) have reversible abnormalities in the sinus cavity in magnetic resonance imaging or x-ray when having a common cold of one week duration. Only a small number of patients, however, develop bacterial sinusitis (Gwaltney Jr, 2005c) and for those that do, the spontaneous recovery-rate is high (62–69%) (Williams Jr et al., 2003). The Finnish treatment guideline for acute maxillary sinusitis recommends antibiotic treatment providing that maxillary effusion is verified (Blomgren et al., 2005). Diagnostic tests and antibiotic treatment should, however, be avoided in patients with sinus symptoms within the first week of common cold.

Otitis media is the most common disease of early childhood affecting three quarters of children by the end of age three (Alho et al., 1991, Teele et al., 1989).

Bacteria are isolated fairly often in middle ear exudates but in spite of it, most patients would recover spontaneously (Glasziou et al., 2004). The problem is how to identify those who would recover well without antibiotic from those who benefit of it. The benefit of antibiotic treatment in acute otitis media has been seriously questioned recently (Glasziou et al., 2004). Watchful waiting with pain relieving medication for 2–3 days is recommended in many countries as a primary strategy in acute otitis media in otherwise healthy children older than two years of age (Van Kuijk et al., 2006). The Finnish guideline recommends antibiotic treatment in acute otitis media providing that middle ear effusion is verified (Puhakka et al., 1999). It does not directly recommend, but accepts also watchful waiting in mild cases.

Acute bronchitis is defined as "a self-limited inflammatory syndrome of the tracheobronchial tree that is most commonly the result of an acute respiratory syndrome" (Gwaltney Jr, 2005a). Cough occurs in approximately 50% of the cases of common cold. Symptoms of acute bronchitis resemble very closely to common cold with cough and the causative agents are mostly the same as well. However, prolonged cough is the predominant symptom in infectious bronchitis, lasting more than two weeks in 45% of cases and over three weeks in 25% of patients (Gwaltney Jr, 2005a, Verheij et al., 1995) and total recovery from the disease normally takes three to six weeks. Treatment with antibiotics has modest or no effect on the resolution of cough or on the course of illness (Fahey et al., 2004, Fahey et al., 1998, MacKay, 1996, Orr et al., 1993). In most countries, including Finland, antimicrobials are not recommended for cases of acute bronchitis in otherwise healthy patients unless there is evidence of bacterial causative agents (Gwaltney Jr, 2005a, Honkanen et al., 1999, WHO Model Prescribing Information, 2001). The key issue mostly is to distinguish those individuals at risk of or having pneumonia.

Table 2. Summary of the most common causative agents and incidence of the most frequent community acquired infections (Adapted from Mandel-Douglas-Bennett's Principles and Practice of Infectious Diseases, 6th Edition, 2005)

Diagnosis	Aetiology	Incidence
Unspecified URTI* (common cold)	Rhinoviruses 30–53 %	Annual attack rate adults 2–4 and children 6–8 per year
	Coronavirus 9–15 %	
	Influenza viruses 6–30 %	
	Parainfluenza viruses 3–5 %	
	Adenovirus 1–10 %	
	Other viruses 2 %	
	Bacteria 4 %	
	Unknown 30 %	
Throat infection	Streptococcus pyogenes group A 15–20 %, groups C and G 5–10 %	
	Viruses 20 %	
	Unknown 30 %	

Acute sinusitis	Streptococcus pneumoniae 20–36 %	Bacterial sinusitis complicates
	Haemophilus influenzae 6–26 %	common cold in 0.5–2 % of cases.
	Moraxella catarrhalis 2–10 %	Annual incidence-rate 2–8%
	Other bacteria 0–10 %	
	None or viral 2–40 %	
Acute otitis media	Streptococcus pneumoniae 27–52 %	By age of two years up to 70 % of
	Haemophilus influenzae 16–52 %	children have had at-least one, and
	Moraxella catarrhalis 2–15 %	every fifth three or more episodes
	Other bacteria 0–24 %	of acute otitis media
	None or viral 12–35 %	
Acute bronchitis	Viruses as above 80 %	Annual attack rate 40–54 per
	Bordetella pertussis 12–32 % (in epidemics)	100000 patients in general practice in UK
	Role unknown:	
	Streptococcus pneumoniae	
	Haemophilus influenzae	
	Moraxella catarrhalis	
Pneumonia	Streptococcus pneumoniae 20–50 %	Occures in 4–6 % of consultations
	Mycoplasma pneumoniae 3–50 %**	with chief complaint of cough
	Clamydia pneumoniae 3–20%**	
	Viruses (influenza-, RS, adeno, parainfluenza) 10–75%**	
Urinary tract infections	Escherichia coli up to 80 %	40–50 % of the female population
	Staphylococcus saprophyticus 5–15 %	will experience a symptomatic
	Enterococci, klebsiella, Pseudomonas, Proteus	urinary tract infection at some time during their life
Bacterial skin infections	Streptococcus pyogenes 20–30 %, (almost always in erysipelas)	
	Staphylococcus aureus 20–80%	

*URTI = Upper Respiratory Tract Infection

**varies according to age and epidemic situation

Pneumonia is still today the most common cause of infection-related mortality in the developed world. Pneumonia is, however, rare among patients having symptoms of upper respiratory tract infection and cough (Donowitz & Mandell, 2005) (Table 2) – except during the influenza season (Korppi et al., 2003). The risk of pneumonia is highest in the very young children and adults aged 60 or more. Other risk-factors are male gender, repeated respiratory infections in children, chronic lung- and cardiac diseases, smoking, dusty work environment and poor social and economic situation (Korppi et al., 2003). Typical symptoms, which refer to pneumonia, are fever, rapid breathing and cough without symptoms of URTI, especially in connection with poor general condition, pleurodynia while breathing and crepitation in auscultation (Korppi et al., 2003, WHO Model Prescribing Information, 2001). If pneumonia is verified

or strongly suspected, Finnish textbooks recommend antibiotic treatment irrespective of whether the causative agent is virus or bacteria (Korppi et al., 2003). Choice of treatment in outpatient care should cover *Streptococcus* and *Mycoplasma pneumoniae.*

Urinary tract infections (UTIs) can be divided into three categories according to site: cystitis or infection of lower urinary tract, acute pyelonephritis (infection in the kidney) and urosepsis i.e. acute infection in the urinary tract with septicaemia (Sobel & Kaye, 2005). Occasional cystitis with otherwise healthy women are called uncomplicated UTIs and can, according to Finnish guidelines, be diagnosed by typical symptoms only and be treated with short courses of antibiotics (Ikäheimo et al., 2000). In all other cases, including UTIs in men, children, pregnant women and hospitalized patients as well as relapsing UTIs in healthy women and complicated UTIs, laboratory diagnostics is recommended and, in most cases, the recommended treatment regimen is different from that of female uncomplicated UTI. Asymptomatic bacteriuria is fairly common in women and elderly men but in most cases does not need treatment. Causative agents in outpatient urinary tract infections (Table 3) are, generally speaking, the same irrespective of the level of infection, patients' age or gender (Sobel & Kaye, 2005).

Bacterial skin-infections are a miscellaneous group of more or less superficial infections which may, however, sometimes lead to even life-threatening, septicaemic erysipelas. In general streptococci are more involved in deeper infections, erysipelas and cellulitis, and staphylococci in superficial infections, but the bacteria may be present also simultaneously (Bernard et al., 1989, Bisno & Stevens, 1996). Other, less common causative agents are not discussed here.

Diagnostics

The clinical pictures of acute respiratory tract infections are closely related and share similar symptoms, pathogenesis and aetiology (Nicholson et al., 1997). All can be caused by viruses, bacteria, or a combination of these. Instead of identifying the specific etiologic agent, the clinician's main problem usually is whether the probable agent is treatable with antimicrobials or not. Clinical signs are in most cases unhelpful, as they differ little in bacterial and other infections. On the other hand, the presence of bacteria does not necessarily correlate to outcome, whether or not appropriate antibiotic is prescribed (Macfarlane et al., 2001). Diagnostic tests can, however, help to achieve a more precise diagnosis than clinical findings alone and thus to reduce unnecessary antibiotic prescribing.

A cloudy, bulging and poorly mobile tympanic membrane in pneumatic otoscopy is usually a sign of bacterial origin (Karma et al., 1989, Rothman et al., 2003, Schwartz et al., 1981). Often, however, neither the circumstances and compliance of the child patient, nor the equipment for pneumatic otoscopy are ideal, leaving the clinician with considerable uncertainty (Blomgren & Pitkäranta, 2003, Blomgren & Pitkäranta, 2005, Rosenfeld, 2002).

24

Tympanometry is a non-invasive, quick, safe, painless and reliable method to reveal whether there is fluid in the middle ear (Finitzo et al., 1992, Palmu et al., 1999). It has been shown to improve the accuracy of diagnosis of acute otitis media in primary care (Blomgren & Pitkäranta, 2003, Green et al., 2000, Johansen et al., 2000, Palmu et al., 1999, Van Balen et al., 1999) and to decrease the number of diagnosis of otitis media remarkably (Blomgren et al., 2004, Johansen et al., 2000).

In sinusitis, clinical signs and symptoms do not provide sufficient information about aetiology (Blomgren et al., 2002, Varonen et al., 2000, Williams & Simel, 1993). Ultrasonography is a quick, painless and safe method which is proved useful in detecting fluid retention in maxillary sinuses (Puhakka et al., 2000) also in primary care, providing that GPs are properly trained to use it (Laine et al., 1998, Mäkelä & Leinonen, 1996, Varonen et al., 2003). Plain radiograph may also be a useful tool in diagnosing sinusitis in primary care. A clear sinus in radiograph rules out sinusitis, while air-fluid level is a relatively reliable indicator of acute sinusitis, but the significance of completely opaque sinus or mucosal swelling is controversial (Axelsson et al., 1970, Kay et al., 1984). The limitations of sinus radiograph are also availability, costs and radiation to eye lenses, especially if needed repeatedly.

In throat infection, no single element of clinical history or physical examination is accurate enough to rule in or out strep throat, but clinical prediction rules have been used to focus the treatment to those who may have a strep throat (Dobbs, 1996, Ebell et al., 2000). Better sensitivity and specificity has been obtained, however, by using the scoring for selection of patients for throat swab and treating only those with positive result in rapid test or culture (Bisno et al., 2002, Ebell et al., 2000, McIsaac et al., 2004).

As the level of C-reactive protein (CRP) is commonly higher in bacterial than in viral infections, it is thought to be useful in differentiating between bacterial and viral aetiology and between pneumonia and bronchitis in community acquired lower respiratory tract infections (Babu et al., 1989, Flanders et al., 2004, Holmberg et al., 1990, Hopstaken et al., 2003, Smith & Lipworth, 1995). Recent studies have challenged this, though (Hopstaken et al., 2005, van der Meer et al., 2005). A high CRP-level seems, however, to help in assessing the severity of lower respiratory tract infections (Seppä et al., 2001). On the other hand, low CRP-level in a patient with prolonged symptoms of respiratory tract infection could support a viral aetiology and help the physician in refraining from prescribing antibiotics (Andre et al., 2004).

The most important differential diagnostic problem in acute bronchitis is pneumonia. There are no individual or combination of clinical findings that could definitely rule in the diagnosis of pneumonia in suspicious cases although absence of any vital sign abnormalities or any abnormalities on chest auscultation substantially reduces the likelihood of pneumonia (Hopstaken et al., 2005, Juven et al., 2003, Metlay & Fine, 2003, Metlay et al., 1997, Wipf et al., 1999). Chest radiography in conjunction with the clinical history and physical examination has been regarded as the 'golden standard' in distinguishing between

pneumonia and bronchitis although its sensitivity is not very high (Syrjälä et al., 1998).

In contrast to respiratory tract infections, typical clinical symptoms and signs rule in the diagnosis of uncomplicated urinary tract infection in women with more than 90% probability (Bent et al., 2002). In a recent placebo-controlled study, symptoms also predicted response to antibiotic therapy better than a negative dipstick result (Richards et al., 2005) thus supporting the practice of empirical treatment of female uncomplicated UTIs.

Antibiotics

Definitions

The Oxford Reference Online defines substances that have a selective toxic action on micro-organisms as follows (www.oxfordreference.com):

Antimicrobials are any type of drugs (natural or synthetic) for killing micro-organisms (bacteria, virus or fungi) or suppressing their multiplication or growth

Antibiotics are substances produced by various micro-organisms that destroy or arrest the growth of other micro-organisms (except viruses)

Antibacterials Are substances that destroy bacteria or suppress their growth or reproduction.

The word antibiotic has been used in this thesis as a general term and the other two as specific terms referring to their real sense.

ATC classification

In the 'Anatomical Therapeutic Chemical' (ATC) classification system the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties (WHO Collaborating Centre for drug Statistics Methodology, 1996, Voipio, 2003). The drugs are classified into groups at five different levels. This classification is used in the national sale statistics and it was used in the classification of symptomatic medication in this study.

The complete classification of amoxicillin (J01CA04) illustrates the structure of the code:

J   Anti-infectives for systemic use
J01   Antibacterials for systemic use
J01C   Beta-lactam antibacterials, penicillins
J01CA   Penicillins with extended spectrum
J01CA04 Amoxicillin

26

DDD unit

Drug consumption is expressed in most statistics using the unit 'Defined Daily Dose' (DDD), which is an internationally agreed drug-specific theoretical (assumed average) daily dose (WHO Collaborating Centre for drug Statistics Methodology, 1996). DDD is a technical expedient and is not necessarily equal to the real dose but it is a uniform measurement for national and international comparison. The DDD of a drug may be problematic to establish as the dose may be different depending on the indication, the patient and differing therapeutic practices in different countries.

Drug consumption is usually expressed in number of DDDs per 1000 inhabitants per day, sometimes expressed as DID. In Finnish statistics on medicines, the calculations are based on the volume of sales to pharmacies and hospitals by wholesalers and the DDD for each drug. The DID of a drug is calculated as follows:

Sales of the drug in grams per year/DDD of the drug in grams
= sales per year in DDDs
DID = (sales per year in DDD / population x 366days) x1000

Some drugs sold from the wholesaler may, however, still be unused either in the pharmacy or in the patients' homes. Further, DDD is calculated in relation to the total population, although the use may be concentrated to certain subgroups in the population. In retrospective comparisons, possible changes in DDD units and ATC classification must also be taken into account. The purpose of the ATC/DDD system is, however, to serve as a tool for drug utilization research in order to improve the comparability of drug use data.

Antibiotic use in community care

Antibiotic use in Finland

In the mid-1960s the governmental health regulatory agency, the National Board of Health (NBH; Lääkintöhallitus), was given a task by law to evaluate, control, survey, monitor and regulate pharmaceutical drugs and their use in Finland (Idänpään-Heikkilä, 1979). Although the law allowed the health authority to request drug sales statistics from manufacturers, wholesalers, pharmacies, and hospitals, in the early years this was done only occasionally due to the enormous work needed to get reliable information. At the same time, however, the manufacturers established a nationwide system of drug sales statistics run by an independent market research institute IMS (International Medical Statistics). In

1973, the pharmaceutical industry agreed that governmental institutions could have access to these statistics. The IMS survey was based on prescriptions delivered from a sample of 62 pharmacies representing the national drug market. Sales to hospitals were not included, this information being collected separately from wholesalers by the NBH. Since 1978 all hospitals had a duty to report their drugs consumption directly to the NBH. Today national statistics are no longer based on IMS surveys, but rather there are two organisations collecting drug sales data: the National Agency for Medicines hosts a sales register based on reports from the wholesalers and the Social Insurance Institution keeps its own records on all reimbursed prescriptions delivered from the pharmacies.

The first national statistics on drug use were published as Nordic reports (Nordic Statistics on Medicines) by Nordic Council on Medicines every third year and until the end of the 1980s they were based on IMS surveys (Westerholm et al., 1979). Since 1987, the National Agency for Medicines and the Social Insurance Institution have produced annual sales statistics, based on their own data, and published them as a book called Finnish Statistics on Medicines (Martikainen et al., 2005). The weakness of these statistics has been that they do not include information on the indication of use of medicines and they do not tell anything about those patients who are not prescribed drugs.

Total sales of antibacterials for systemic use (ATC-code J01), in deflated retail price, amounted in 1998 to EUR 111 million (662 million Finnish marks; deflated to year 2004 level by consumer price index/health care) and EUR 97 million in 2004. Of this amount 59% in 1998 (EUR 65 million) and 57% in 2004 (EUR 55 million) were used in outpatient care. When measured in defined daily doses (DDD) the proportion of outpatient use was, however, higher, at 86% in 1998 and 83% in 2004, which means that the total human antibiotic burden in society is more determined by outpatient than by hospital use. To arrive at the total antibiotic volume in the society, antibiotic use in the animal livestock industry and animal veterinary have to be added, which in 1997 was about 29% of the total antibiotic use for veterinary medicine and 7% for animal feed additives (Bakteerien lääkeresistenssin torjuminen ja mikrobilääkepolitiikan kehittäminen -työryhmä, 2000). Since then antibiotic use in feed additives has been abandoned in Finland.

Annual sales of antibacterials (including methenamine and nitrofurantoin) in Finland have shown a slowly declining trend since the beginning of the 1990s (Figure 3). Outpatient antibiotic sales have decreased 18.7% between 1993 and 2004 (3.9DDD/1000 inhabitants/day, from 21.0 to 17.1). There was already a decline of 12.8% from 1993 to 1998 i.e. before the MIKSTRA programme started, and since then an additional decrease of 5.9% from 1998 to 2004, which was more emphasised in the last couple of years. In the same time period, sales of antibacterials to hospitals have increased, however, by 35%.

Figure 3. *Annual sales of antibacterials for systemic use (J01, including methenamine and nitrofurantoin) in Finland 1993–2004 (Source: Finnish Statistics on Medicines)*
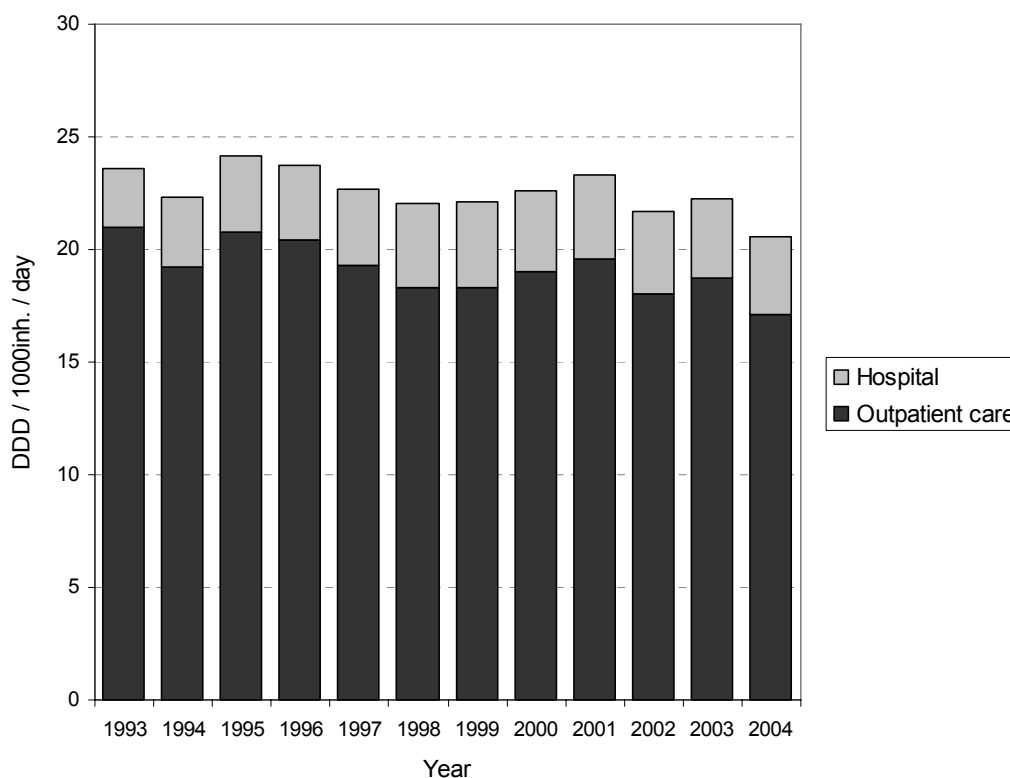
The declining trend in antibiotic sales in Finland is evident in most antimicrobial classes. The decline has been steady throughout the follow-up period in doxycycline, penicillin-V and fixed sulfa-trimethoprim combinations (Figure 4). The rapid increase in the use of cephalosporins in the beginning of the 1990s peaked in 1995 and it has been slowly declining since. The use of erythromycin fell drastically between 1991–92 when its use was restricted in throat infections because of increased resistance among group A streptococci (Huovinen & Klaukka, 1991, Seppälä et al., 1992). With the emergence of the new macrolides, roxithromycin, azithromycin and later clarithromycin, marketed for use in respiratory infections other than throat infection, the use of this group has been constantly rising until 2004. Amoxicillin, with and without clavulanic acid, as well as quinolones, have also largely seen a trend of increasing use, though with a slight decline in 2004.

Figure 4. *Antibiotic sales by group in Finland 1990–2004 including both hospital and outpatient care (Source: Finnish Statistics on Medicines)*
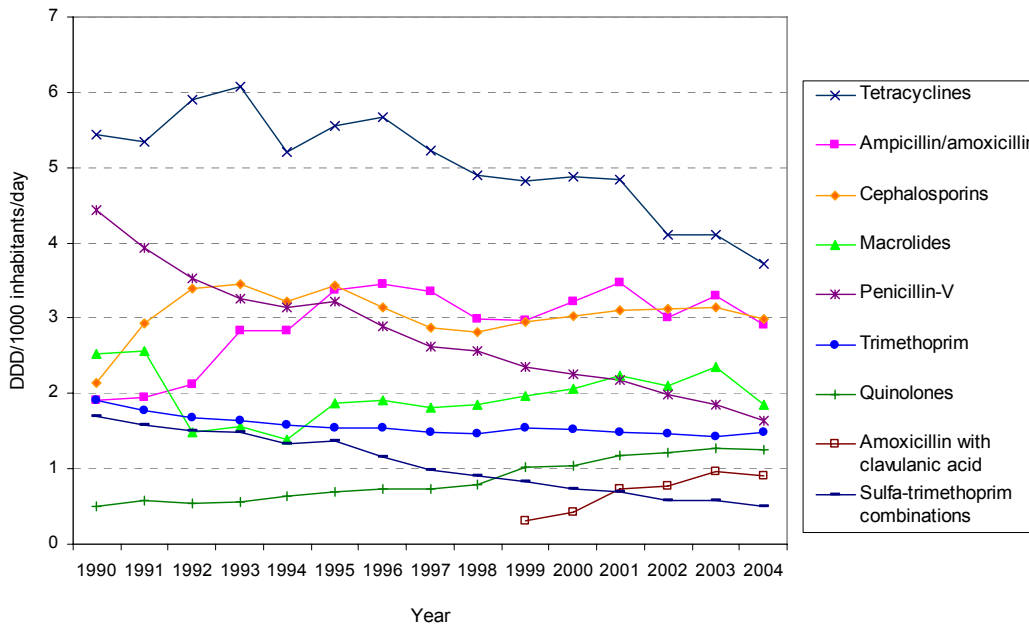
Comparison to other countries

Finland and Iceland have traditionally had the highest consumption of antibiotics among the Nordic countries, followed by Greenland (Nordic Medico-Statistical Committee, 2004). According to NOMESCOs report, in 2003 total consumption of antimicrobials for systemic use (ATC-group J01), including both outpatient and hospital sales, was highest in Finland (22.3 DDD/1000 inhabitants/day), while in Denmark it was 33% lower (15.0), in Sweden 27% lower (16.3), in Norway 23% lower (17.1), and in Iceland 9% lower (20.3). There are probably no true differences in the incidence of common infections between these countries, but the differences in antibiotic use derived more from diverging practices and guidelines. In Norway and Iceland antimicrobials are reimbursed only in long-term treatment. In Denmark tetracyclines and cephalosporins are not reimbursed and their use was 1/4 and 1/15 of the use in Finland, respectively. Sweden and Finland reimburse antimicrobials but in many cases the expenditure will be too low to be eligible for reimbursement after the patient's own contribution.

A similar decline as in Finland was seen in Sweden between 1993 and 2004 in outpatient antibacterial sales (-22%, from 18.7 to 14.7DDD/1000 inhabitants/day) and the major part of it took place before 1998 (Cars & Ekdahl,

30

2003, Cars & Olsson-Liljequist, 2005). Outpatient antibiotic sales data is not available before 1997 from other Nordic countries. However, in Denmark outpatient consumption of antibacterials has increased 10% between 1998 and 2004 (from 12.8 to 14.1DDD/1000 inhabitants/day) (Emborg et al., 2005) and in Norway, total human antibacterial sales have increased 4% between 1998 and 2004 (from 16.6 to 17.2DDD/1000 inhabitants/day) (NORM/NORM-VET 2004, 2005), while in Iceland it has decreased 12% between 1998 and 2003, from 23.0 to 20.3 DDD/1000inhabitants/day (Ministry of Health and Social Security Iceland 2004). Bigger reductions have been reported from other countries for outpatient antibiotic prescriptions for acute respiratory tract infections in children: in England a reduction of 8% from 1994–1998 (Unsworth & Walley, 2001) and 45% from 1994–2000 (Ashworth et al., 2004), in Canada 30–40% from 1995 to 2001 (Kozyrskyj et al., 2004) and in the USA 16–25% from 1996–2000 (Finkelstein et al., 2003) and 40% from 1989/90 to 1999/2000 (McCaig et al., 2002). At the same time these, and some other studies (Ashworth et al., 2005, Fleming et al., 2003, Fleming et al., 2005), have found a remarkable decline (from 7% up to 48%) in the consultation rate in primary care for mild respiratory tract infections, referring to a simultaneous change in patient behaviour.

According to NOMESCOs report, in 2003 the penicillin group (J01C) constituted about half of all antimicrobial consumption in all other Nordic countries except Finland, where it accounted for 28% of total sale. Use of teracyclines almost reached that of penicillins in Finland, being as popular only in Iceland and even more popular in Greenland.

What appears typical of Finnish antibiotic consumption, compared to other Nordic countries, is also a favouring of cephalosporins and broad-spectrum instead of narrow-spectrum penicillins. Penicillin-V was used in Denmark almost three times more and in other Nordic countries more than twice more than in Finland. Correspondingly, we used amoxicillin twice as much as in Sweden and a third more than in Norway, and amoxicillin with clavulanic acid also five to ten times more than in other Nordic countries – except for Iceland, where its use is even more popular than in Finland. Our use of cephalosporins is quite unique among Nordic countries, 4.5–30 times more than in any of these countries.

The antibiotic group J01E, including both sulfa and trimethoprim products, was used in Finland and Iceland twice more than in other Nordic countries. Of the total sales of the group J01E antibiotics in 2003, pure trimethoprim comprised 71% in Finland and 75, 69, 49 and 42% in Sweden, Norway, Denmark and Iceland respectively. Sales of quinolones were also twice as high in Finland and Sweden as in other Nordic countries.

Two recent studies have compared antibiotic sales in European countries (Cars et al., 2001, Goossens et al., 2005). In these comparisons Finland is situated in the mid-point with Iceland, while other Nordic countries are among the low consumers (Figure 5). In 2002, we used almost twice as much antimicrobials as was used in the Netherlands, but about one third less than that used in France or Greece.

In respect of the use of narrow-spectrum penicillin, Finland is situated in the second highest quartile in the European comparison and in the second lowest quartile in respect of macrolide and quinolone consumption (Goossens et al., 2005). Sulfa and trimethoprim-group (J01E) is used only in Croatia and Czech Republic in an equivalent amount as in Finland and Iceland, but the information on the proportion of trimethoprim within the group is not available from these countries.

Figure 5. *Total outpatient antibiotic use in 26 European countries in 2002 (Source: ESAC, European Surveillance of Antimicrobial Consumption)*
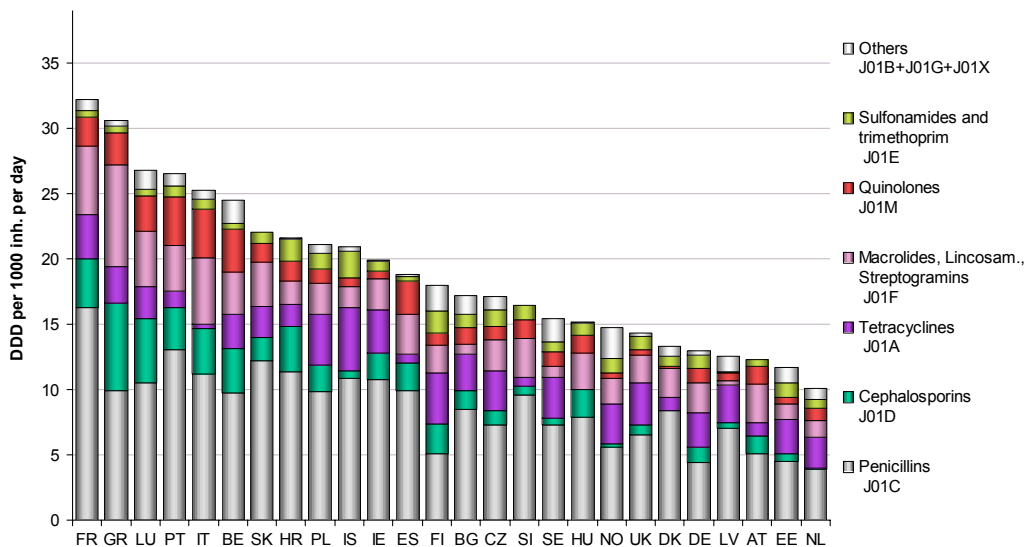
In a European context, Finnish cephalosporin use was by comparison no longer exceptionally high. Compared to the very high cephalosporin consumption countries, Greece, Luxembourg, France, Italy, where first generation cephalosporins comprised less than half of this group, the proportion of first generation use in Finland was over 90 per cent (Goossens et al., 2005, Molstad et al., 2002), whish may be favourable from the point of view of development of bacterial resistance.

It is difficult to compare European consumption to that on other continents, because most countries outside Europe seem to favour reporting the numbers of prescriptions per population instead of DDDs. In an Australian report from 1994, total antibiotic consumption in Australia mounted to about 25 DDD/1000 inhabitants/day, in the USA to 23 and in Canada about 20 (McManus et al., 1997). These figures were based on IMS surveys.

Problems related to antibiotic use
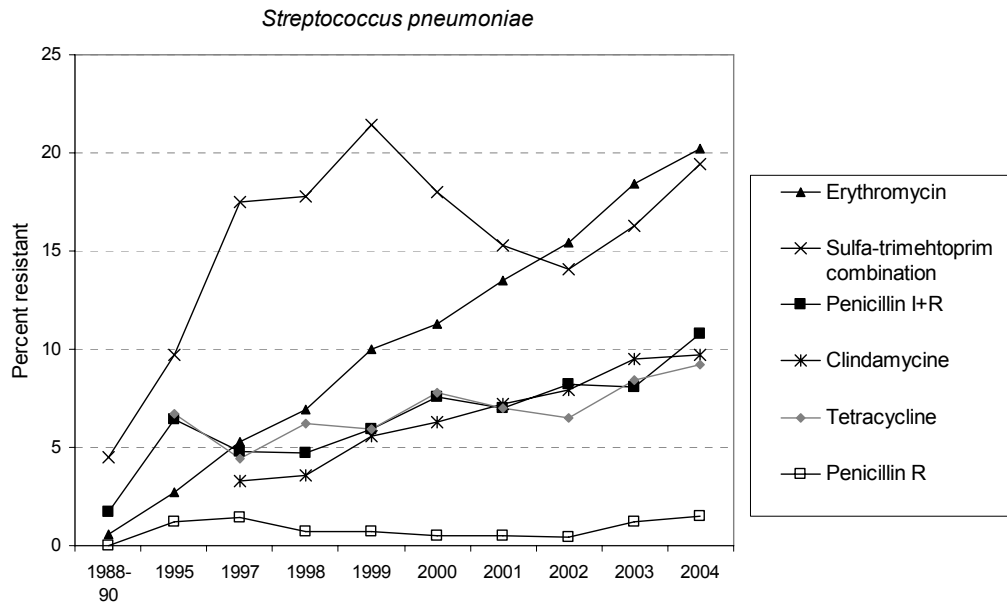
Resistance

The correlation between resistance and community antimicrobial use is established in many connections (Steinke & Davey, 2001), in Finland (Bergman et al., 2004, Nissinen et al., 1995, Pihlajamäki et al., 2001, Seppälä et al., 1995), in other countries (Arason et al., 1996) as well as in multinational studies (Albrich et al., 2004, Bronzwaer et al., 2002, Goossens et al., 2005). Not only the volume of antibiotic use but also the selection of broad-spectrum drugs, low dose, and long duration of antimicrobial treatment increases the emergence of resistance (Guillemot et al., 1998, Hay et al., 2005, Livermore, 2005, Odenholt et al., 2003).

Population density seems to have a role in the spread and carriage of antibiotic resistance (Bruinsma et al., 2003, Huang et al., 2004). The increase of the resistance problem during recent years may partly be related to not only the increasing use of broader spectrum antibacterials, but also crowding the most vulnerable members of society in day care centres (Dunais et al., 2003, Herruzo et al., 2002, Kristinsson, 1995, Melander et al., 1998, Mölstad et al., 1988, Reichler et al., 1992) and nursing homes (Leistevuo et al., 1996, Nuorti et al., 1998). The efficiency of increasing international travel to spread resistant strains far from their point of origin has also been shown (Soares et al., 1993, Stingemore et al., 1989).

Antimicrobial resistance of the bacteria causing common infections in the community has been fairly low and stable in Finland. Since the peaking at over 15% in 1992–94 and 1998 the resistance of *Streptococcus pyogenes* to erythromycin has been less than 10%, and during the past three years even less than five per cent. Resistance of *Haemophilus influenzae* to ampicillin and sulfatrimethoprim has been declining slightly since the end of the 1990s, being at less than 20% and 15% respectively, while it is still sensitive to tetracyclines and kefuroxime. *Moraxella chatarrahlis,* on the other hand, is practically resistant to ampicillin but sensitive to all other commonly used antibacterials. Oxacillin-resistant strains of *Staphylococcus aureus* have increased four fold since 1998, but their proportion is still below five per cent, while that of erythromycin resistance has reached six per cent. The proportion of ampicillin and trimethoprim resistant strains of *Escherichia coli* have been declining, but are still fairly high, at around 22% and 17% respectively, while resistance to mecillinam, nitrofurantoin and quinolones is very low.

The development of the antibacterial resistance of *Streptococcus pneumoniae* has, however, been worrying. There has been an increasing trend in resistance to all commonly used antibiotics except in high-level penicillin resistance (R) of this bacteria and the increase has been especially steep with erythromycin (Figure 6).

Figure 6. *Antibacterial resistance of Streptococcus pneumonia in Finland 1988–2004 (R=resistant, I=reduced susceptibility) (Source: FiRe, Finnish Study Group for Antimicrobial Resistance, 2005)*

Streptococcus pneumoniae

There are several reasons to be especially concerned about the high level (20.2%) of macrolide resistance. Firstly pneumococci are the potentially most 'dangerous' pathogens causing community acquired infections that can be severe. Secondly, macrolides are often used as first- or second-line drugs in outpatient care for infections suspected to be caused by pneumococci, including pneumonia. Thirdly, in-vitro macrolide resistance of pneumococci is almost always clinically relevant and may lead to serious treatment failures (Koivula et al., 2004, Rothermel, 2004, Rzeszutek et al., 2004, Yu et al., 2003) while at-least intermediate penicillin resistance (I) can in most cases be tackled by high dosing of penicillin (Rothermel, 2004, Yu et al., 2003). Furthermore along with increasing macrolide resistance, a simultaneous resistance to penicillin and the multiresistance of pneumococci has also increased (Bruinsma et al., 2004, Pihlajamäki et al., 2002).

It has been suspected that the new generation macrolides with a long half-life might be more prone to promoting resistance than the older shorter half-life macrolides by allowing sub inhibitory serum and epithelial lining fluid concentrations for several weeks after treatment (Baquero, 1999, Heuer & Larsen, 2004, Kastner & Guggenbichler, 2001). These macrolides have been increasingly favoured in the treatment of paediatric upper respiratory tract infections in Finland.

34

In a European comparison of the proportions of erythromycin-resistant pneumococci in invasive infections, Finland is situated in the moderate group along with Middle European countries, while other Nordic countries belong to the group of low-level resistance (Figure 7).

Figure 7. *Proportion of erythromycin non-susceptible Streptococcus pneumoniae isolates in 28 European countries in 2004 (Source: EARSS, European Antibiotic Resistance Surveillance System)*
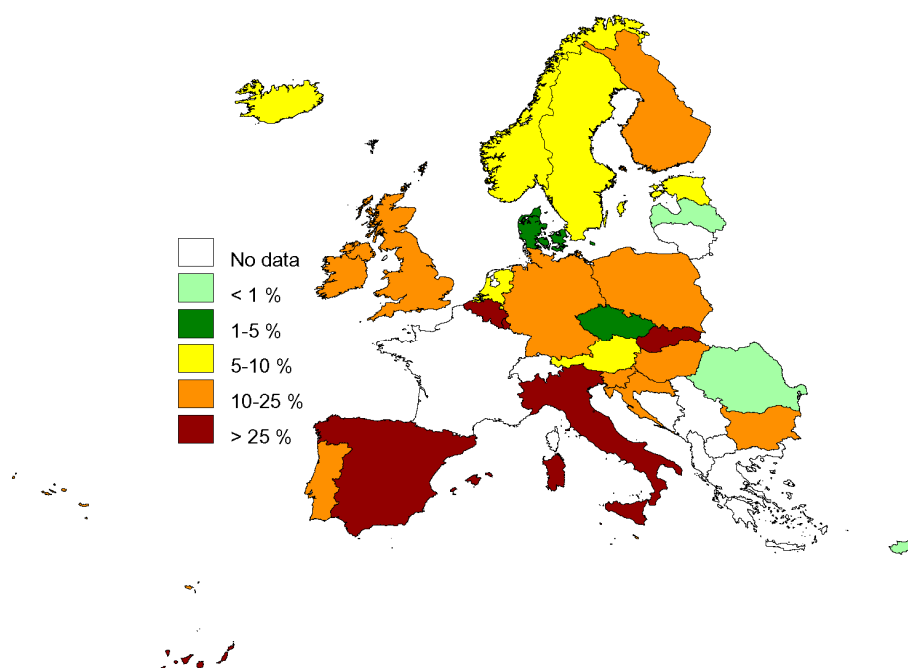
In Sweden there has been more or less a similar trend over the years in the development of resistance of pneumococci, although at a lower level than in Finland. Proportions of non-susceptible strains (I plus R) to penicillin and erythromycin have been slowly increasing, but remained below six per cent, while the rising trend seemed to be broken in 2004 (Cars & Olsson-Liljequist, 2005). Even in Denmark, resistance to penicillin and erythromycin of invasive isolates of *Streptococcus pneumoniae* have increased from about one per cent in 1995 to two per cent and five per cent in 2003, respectively, but since then both seem to be declining (Emborg et al., 2005). In Norway pneumococcal resistance to erythromycin has begun to rise steeply since 2001, being 9.7 per cent in 2004, while the proportion of penicillin non-susceptible strains (I+R) has decreased remarkably from around 7 per cent in 2000, remaining below 2.0 per cent since then (NORM/NORM-VET 2004, 2005).

The prevalence of pneumococci with reduced susceptibility to penicillin and erythromycin varies markedly around the world. According to an international,

commercially funded Alexander Project's report from years 1998–2000, covering centres from 26 countries around the world, the world-wide prevalence of penicillin-R strains of pneumococci isolated from community acquired respiratory tract infections, was 18.2 and that of erythromycin-R strains 24.6 (Jacobs et al., 2003). An extremely high prevalence of penicillin resistance has been found in France (40.5) and some Far East countries, for instance in Hong Kong (69.9). A prevalence exceeding 20 per cent is seen in many countries including Ireland (24.1), Spain (26.4), Israel (29.7), Japan (28.5), Singapore (24.8), Mexico (22.2) and the USA (25.0). Correspondingly, erythromycin resistant strains of pneumococci are most prevalent in countries with high a prevalence of penicillin resistance, i.e. Hong Kong (80.3), Japan (71), France (53.2), Singapore (37.8), USA (28.8) and Spain (27.5), but also in some countries with lower penicillin resistance like Italy (35.2), Belgium (23.9) and Greece (23.2). Corresponding levels of resistance are measured in other studies, for example in the USA in resistance to penicillin (Whitney et al., 2000) and macrolides (Hyde et al., 2001), and for macrolide resistance in Canada (12–16%) (Conly, 2002).

It seems that the time scale for emergence of bacterial resistance under selective pressure is much shorter than the reversion time after cessation or decline in the volume of drug use. To obtain a significant reduction in resistance demands as significant a reduction in drug use, and preferably at as an early stage as possible (Austin et al., 1999, Cars, 2001). For instance in a study made in rural Alaska, a one-third reduction in antibiotic courses per person did not decrease the carriage of penicillin non-susceptible strains in the community within two years (Hennessy et al., 2002).

A decline in resistance after a decrease in antibiotic consumption in the community has so far been shown only in a few cases. In Finland, a two-thirds reduction in erythromycin use for tonsillitis was followed by a decline in the frequency of erythromycin resistant group A streptococci, with a delay of a few years (Seppälä et al., 1997). In Iceland, a recommendation to reduce antibiotic prescription for otitis media was given in 1991 because of the steep increase in the proportion of multiresistance among pneumococci. Total antibiotic sale decreased 10% but that of sulfatrimethoprim and erythromycin fell 30% while the proportion of resistant streptococci peaked in 1993 but declined only thereafter (Kristinsson, 1997). But, as bacterial resistance is a complex issue, even substantial reduction in drug use does not necessarily lead to reduction in resistance. This was experienced in the UK, where the proportion of sulphonamide resistant *Escherichia coli* has remained high in spite of over 90 per cent reduction in the use of sulphonamide (Enne et al., 2001). It has been speculated that this might be due to continued use of this drug in the livestock industry (Livermore, 2005).

36

Disturbance of normal microbiota

In recent years an increasing number of published studies suggest that antibiotics may have many harmful effects on health through the disturbance of human microbiota. Antibiotic treatment seems to predispose to new infections. In the USA, young women were discovered to be more prone to get a cystitis 15–28 days after a course of antibiotic (Smith et al., 1997). Howard et al. had noticed already in the 1970s that when acute otitis media is treated with broad-spectrum antibiotic it relapses more probably than after a course of narrow-spectrum antibiotic (Howard et al., 1976). The incidence of recurrent acute otitis media has increased three-fold in Finland from 1978/79 to 1994/95 and at the same time penicillin-V has been replaced with antibacterials with broader spectrum as the first-line drug without any obvious change in microbial ecology that would justify the shift (Joki-Erkkila et al., 2000). The researchers speculated that suppression of normal bacterial flora during a course of antibiotic could give pathogens better conditions and thus would predispose to a new infection. This hypothesis gets support from a reverse finding in a recent five-year follow-up study from Iceland, which reported that in the regions where antibiotic prescribing was restrictive at the baseline in 1998, antibiotic prescribing for otitis media further decreased and at the same time the proportion of tympanostomy tube placements diminished from 26% to 17% (Arason et al., 2005). In the originally high-prescribing regions, however, the development was the opposite: prescribing for otitis media further increased and tympanostomy tube placements increased from 35% to 44%. Further, Margolis et al. have found that the odds of getting an URTI is two times greater with patients receiving oral antibiotic treatment for acne, which frequently continues for several months though, compared with those who do not use antibiotics (Margolis et al., 2005).

There are several studies referring to still inconclusive connections between antibiotic use and some chronic diseases and cancer. Enterolactone is a health promoting substance produced by gut bacteria from lignans received from whole grain foods, fruits and vegetables. Vanharanta et al. showed that men with higher serum concentration of enterolactone had a lower risk for acute coronary events (Vanharanta et al., 1999). Later it has been shown that use of oral antimicrobials decreases serum enterolactone concentration (Kilkkinen et al., 2002), but the connection between antibacterial use and risk of coronary events needs further studies.

Some studies have found connections between long-term antibacterial treatment and increased risk of breast cancer (Knekt et al., 2000, Velicer et al., 2004), and frequent antibiotic use (more than 10 times during adulthood) and non-Hodgkin's lymphoma (Chang et al., 2005), but also these results are still inconclusive.

Temporary diarrhoea and other abdominal symptoms are common side-effects during antimicrobial courses. However, it has been shown that also symptoms of irritable bowel syndrome are three times more prevalent in those who have received antibiotics within four months (Maxwell et al., 2002). In

addition there are several other conditions where disturbance of gut flora is suspected to have had a connection, including kidney stones, liver cirrhosis and even autism and Alzheimer's disease.

Antibiotic policy

General aspects

As antimicrobial use and antibacterial resistance go hand in hand, making antibiotic policy is equal to combating antimicrobial resistance. It has been said that antimicrobial resistance is one of the most important public health concerns of modern times (Carbon et al., 2002). From the beginning of the 1990s a growing concerns about the problem have been presented, first in the USA and gradually also in Europe. Towards the end of the 1990s pressure was increasing to start doing something on the issue. This pressure led to simultaneous actions in different parts of the western world. Within the same year, 1998, the WHO arranged two meetings dealing with antimicrobials in animal husbandry, while a report was published by Britain's House of Lords on antimicrobial resistance (House of Lords Selected Committee on Science and Technology, 1998) and a strategic plan was developed by the US Institute of Medicine on emerging infections and resistance (http://www.cdc.gov/ncidod/emergplan/1toc.htm), an EU Conference entitled 'The Microbial Threat' was arranged in Copenhagen (European Union Conference 'The Microbial Threat', 1998) – and the MIKSTRA programme was started in Finland.

Bacterial resistance is an extremely complex, multidimensional, multidisciplinary and an international issue. It involves basic researchers as well as the general public, hospitals and primary care, preventive and curative medicine, human and veterinary medicine, continuing medical education of professionals as well as educating the public, and even food production, animal husbandry and the pharmaceutical industry. It was estimated, that in the USA in the mid-1990s up to 75% of total antibiotic use could have been questionable (Table 3; adopted from (Wise et al., 1998)). Today, the most questionable use of antibiotics as growth promoters has been abandoned in the EU, and prophylactic use has decreased also substantially.

Because of its complex nature, tackling antimicrobial resistance and developing antibiotic policy needs co-operation between several authorities, organisations, and fields of expertise and the success depends on co-ordination and focus.

Table 3.   Total use of antibiotics in the USA in the 1990s

Where antibiotics are used	Type of use	Questionable use
Human use 50%	Hospital 20% Community 80%	20–50%
Agricultural use 50%	Therapeutic 20% Prophylactic/growth promotion 80%	40–80% highly questionable

The EU Conference 'The Microbial Threat' in September 1998 was one of the first attempts to define European recommendations to combat antimicrobial resistance. The conference outcome was 'The Copenhagen Recommendation' (European Union Conference 'The Microbial Threat', 1998) giving guidelines to the EU and its member states on activities that should be launched. These recommendations were as follows:

- The EU and its members states should recognise that antimicrobial resistance is a major European and global problem
- The EU and its members states should set up a European surveillance system of antimicrobial resistance
- The EU and its members states need to collect data on the supply and consumption of antimicrobial agents in both human and veterinary fields
- The EU and its members states should encourage the adoption of wide range of measures to promote prudent use of antimicrobial agents
- The EU, members states, and national research councils should give a high priority to co-ordinated research on antimicrobial resistance
- The pharmaceutical companies should be encouraged to develop new antimicrobial agents
- A way should be found to review progress with these proposals

A lot of progress has been made since then, as was reported in a follow-up conference held in Visby in June 2001, (Socialstyrelsen, 2001). The European Antimicrobial Surveillance System, EARSS (www.earss.rivm.nl) covers today 31 European countries and the European Surveillance of Antimicrobial Consumption ESAC (www.esac.ua.ac.be) receives antimicrobial consumption figures from 34 countries. Several programmes, task forces, strategies and recommendations have been launched in Europe, in Canada, the USA, and Australia, as well as in the EU and by the WHO (Carbon et al., 2002, WHO, 2001). However, the fact that rates of resistance among common bacteria are still

increasing clearly further emphasises the need for additional efforts on national and international levels. The latest step in the field is the establishment of a European Centre for Disease Prevention and Control ECDC in spring 2005 (www.ecdc.eu).

Optimising antibiotic use

Guidelines and their implementation

Along with the development of technology, new research evidence has begun to increase exponentially and textbooks alone are no longer sufficient to update a clinicians' knowledge and skills. In 1980s specialist organisations became increasingly interested in producing clinical treatment guidelines. Already in 1996, over 700 guidelines had been published in Finland since 1989 by local, regional and national bodies on different topics in medicine (Varonen & Mäkelä, 1996). The guidelines varied greatly, however, in volume, coverage and used evidence. The situation was similar in many other countries (Mäkelä, 1996) Editorial).

Modern information technology – besides prompting an explosion in the volume of new research evidence – enabled a more structured processing of the available information. The Cochrane Collaboration was one of the first to create a systematic, rigorous system to summarise the evidence (Chalmers et al., 1992). This working method was applied by the Dutch College of General Practitioners in the beginning of the 1990s to produce more practically oriented guidelines and this same method has been adopted and further modified in at least 18 other countries, including Finland, since then (Burgers et al., 2003).

Practice guidelines are defined as "systematically developed statements to assist the practitioner and patient in decisions about appropriate health care for specific clinical circumstances" (Thorsen & Mäkelä, 1999). In practice, guidelines are meant to help the professionals in diminishing variation and promoting effectiveness in clinical practice and thereby improving the quality of health care. They also help the clinician in keeping up-to-date with the fast growing volume of new research evidence and controlling the increasing costs of health care. Unfortunately however, the mere existence and dissemination of a guideline does not usually change practices, even though it may raise awareness of the issue. Moving from awareness to a change of behaviour requires something further, as changing professional practice has proved to be a complex and often difficult task.

Changing professional practice

Professional behaviour is influenced not only by knowledge, beliefs, and attitudes, but also by other important factors such as the organisation, economy, and community. Any attempt to bring about a change should be a systematic approach and start with a 'diagnostic analysis' to identify factors likely to influence on the change (NHS Centre for Reviews and Dissemination, 1999). Obstacles and opportunities in one setting may not be present in another. The analysis might include 1) an identification of all groups involved in, affected by or influencing the proposed change, 2) an assessment of the characteristics of the proposed change that might influence its adoption, 3) an assessment of the preparedness of the health professionals to change as well as other potential internal barriers within the target group, 4) an identification of possible external obstacles to change, and 5) an identification of the likely enabling factors, including resources and skills. The choice of which intervention to implement should then be based on the 'diagnostic analysis' and knowledge of relevant research.

Passively disseminating recommendations or guidelines may raise awareness and even a questioning of the existing management, but in most cases achieving real change in practice has demanded a multifaceted approach. The success of implementing guidelines has been analysed recently in two large systematic reviews (Grimshaw et al., 2004, NHS Centre for Reviews and Dissemination, 1999). Both report that continuing medical education by means of educational outreach, opinion leaders, patient-mediated interventions and reminders have been fairly successful. Results have been even better if several means have been combined. Mailed educational materials or general feedback have generally not been effective alone, but combining them with educational outreach or an audit has changed behaviour. Targeted recommendations and interventions have also been more successful than general ones. In most cases, however, improvement in care has been modest to moderate with a median effect of 6.0 to 14.1% (Grimshaw et al., 2004). A systematic approach to changing professional practice should also include a monitoring and evaluation system and a plan for maintaining and reinforcing the change.

Reasons for nonadherence to guidelines and barriers of change

Models of change can be used both to understand the behaviour of health professionals and to guide the development and implementation of interventions (NHS Centre for Reviews and Dissemination, 1999). According to 'Learning theory', the probability of behaving in a particular way tends to increase when that behaviour is followed by positive consequences (reinforcement) and tends to decrease when followed by negative consequences. The effectiveness of reinforcing factors depends on how desirable they are, i.e. to which degree the individual is motivated to gain them. If the individual lacks this motivation, there

is little chance of behaviour change. Interventions based on learning theory have been used to change practice, for example through audit and feedback, fee-for-service or lower insurance premiums.

In contrast to learning theory, 'social cognition models' see factors, such as beliefs, attitudes and intentions, as central influences in shaping behaviour. In particular three sets of beliefs have emerged as important in determining behaviour: perceived benefits weighed against perceived barriers (i.e. improved patient outcome versus costs), perceptions about the attitudes of important others to the behaviour (opinion leaders, patients), and the belief in one's ability to perform a particular behaviour. Modifying these factors assists in changing the behaviour.

Like individuals, organisations are also thought to move through a series of stages in the process of change. This 'organisational model' includes three stages: questioning the old behaviour, changing to a new position and reconsolidation of new attitudes, practices, or policies. This approach emphasises the complexities of organisations and individuals as members of them, and the need to take account of the internal and external environments that the individuals are practicing in.

Health professionals' adherence to guidelines may be hindered by a variety of obstacles. A lack of awareness and lack of familiarity can affect health professionals' knowledge of a guideline (Cabana et al., 1999). In addition health professionals may not agree with the specific guideline or the concept of guidelines in general or they may not believe in their ability to actually perform the procedure demanded in the guideline. The professionals may not believe that the recommendation will lead to an improved outcome or they may not have sufficient motivation to change.

Despite an appropriate attitude and knowledge, a professional may encounter barriers that limit his/her ability to perform the recommended behaviour due to the patient, the guideline itself or environmental factors. Patients may be resistant or perceive the recommendation even as offensive or embarrassing. A guideline may be too complicated or the expected change too radically different from previous performance or it cannot be experimented first on a limited number of patients to see whether it is feasible or acceptable. Adherence to guidelines may also require changes not under an individual professional's control, such as new resources or facilities to ensure proper follow-up or diagnostics.

The decision to prescribe antibiotic or not includes a lot of uncertainty, which makes the decision uncomfortable and doctors, like any people, have individually different abilities to tolerate uncertainty (Bradley, 1992b, Logan & Scott, 1996). Especially in respiratory tract infections, which share much the same symptoms, there is often substantial uncertainty about the exact diagnosis and more so about the causative agent (Pichichero, 1999). There may be fear of a poor clinical outcome or medico-legal implications based on personal or colleagues' experience (Pétursson, 2005). For instance, consequences of not treating a potential case of pneumonia may feel more risky than prescribing

42

antibiotic 'just in case'. Doctors may treat not only their patients but also their own anxiety (Pétursson, 2005).

On the other hand, in their desire to be proved 'up to dated' doctors tend to use newer agents, which in most cases are broader spectrum and more expensive than the cost-effective and well documented older ones. This is even supported by an active marketing of newer and more profitable substances by the pharmaceutical industry. Doctors commonly mention commercial information among the four most important sources of drug information (Peay & Peay, 1984, Ziegler et al., 1995). Direct contacts between pharmaceutical sales representatives and doctors, although a rather expensive means of marketing, are obviously quite efficient as it is so common. In the USA there is one pharmaceutical sales representative per 15–30 practising doctors, in Germany one per 21 and in Finland one per 30 doctors (Wallenius et al., 1997). During October 1994 there was on average one visit by pharmaceutical sales representative per working day in 15 health centres in the county of Pirkanmaa (Klaukka & Rautakorpi, 1995). Antibiotics were discussed in every fifth demonstration and most commonly presented substances were cephalosporins, broad-spectrum penicillins, and macrolides. In another Finnish survey (Ala-Fossi, 1997) GPs had 3–4 visits of pharmaceutical representatives per week, while gynaecologists had only one. In the Åland Islands, an autonomic group of islands between the Finnish continent and Sweden, pharmaceutical consumption is lower, while less-expensive drugs are favoured compared to other parts of Finland. One reason for this, according to local doctors, may be that visits of pharmaceutical representatives are cut to one per week (Lahnajärvi et al., 1997). Drug marketing and consumption seem to have other kinds of correlation as well. It was pointed out in a recent European study that there is a quantitative relationship between the number of marketed trade names of antibiotics in a country and consumption in the community (Monnet et al., 2005). Bringing a new, cheaper alternative to market activates competition and marketing and thus increases the total sale of the compound.

One of the factors coming up in most studies exploring general practitioners' decision-making is the perceived patient demands and doctors' desire to perceive the doctor-patient relationship; "if I don't prescribe, the patient goes to another to doctor and gets it anyway" (Bradley, 1992a, Bradley, 1992b, Butler et al., 1998, Howie, 1983, Mangione-Smith et al., 1999, Pichichero, 1999, Schwartz et al., 1989). It seems, however, that patient satisfaction may be more related to receiving information and time spent listening to the patient than receiving a prescription (Brody et al., 1989, Gonzales et al., 2001, Hamm et al., 1996, Himmel et al., 1997, Lundkvist et al., 2002, Welschen et al., 2004a). Also in a theme interview conducted in a population survey in Finland in 1995 most interviewees said that when consulting a doctor for an infection, they do not primarily expect to get an antibiotic, but rather to find out what illness they have (Tuomainen et al., 1995). Similar results regarding patient expectations were obtained in the interviews done by Butler et al. (Butler et al., 1998).

A fear that refusal to prescribe would increase the workload by adding re-consultations is also often brought up by doctors. Research findings however do not support this fear in most cases. In several studies patients who have been sufficiently informed have not re-consulted more often even if they did not get antibiotic prescription (Gonzales et al., 1999, Hueston et al., 2000a, Macfarlane et al., 2002), although results have been contradictory in the case of acute lower respiratory tract infections (Gonzales et al., 1999, Little et al., 2005). In some studies the situation has even been the opposite, with high-prescribing doctors having had higher re-consultation rates (Little et al., 1997, Watson et al., 1999).

Interventions directed to antibiotic prescribing

A range of interventions have been successful in changing antibiotic prescription. In a Canadian study a modest increase of 2.6% versus decrease of -1.7% in control group was achieved in first-line antibiotic use for any infection after individually tailored feedback and repeated mailed bulletins for six months period (Hux et al., 1999). An intervention in Norway focusing on selecting trimethorpim instead of sulfa or sulfatrimethopim in UTI achieved significant change towards the recommendation (Rokstad et al., 1995). However, interventions based on similar mailed prescriber feedback and guidelines did not have an effect on antibiotic prescription rates or the proportion of narrow-spectrum antibiotics in Denmark (Söndergaard et al., 2003) or on the total antibiotic prescription rate in Australia (O'Connell et al., 1999). Interventions based on audit, group discussions and treatment recommendations have resulted in reductions of antibiotic prescription and increases in the prescribing of recommended drugs as well as in the use of recommended diagnostic tests (Melander et al., 1999, Munck et al., 1999).

Intervention studies using continuing medical education by means of educational outreach combined with guidelines (Avorn & Soumerai, 1983, Ekedahl et al., 1995, Perez-Cuevas et al., 1996) and feedback (Lundborg et al., 1999, Zwar et al., 1999) have achieved significant improvements in prescribing. A significant reduction in antibiotic prescriptions for respiratory tract infections and the quality of treatment prescribed have also been achieved by computerised point-of-care evidence-based message systems (Christakis et al., 2001) as well as with computerised or paper versions of clinical-decision-support systems or flowcharts (Samore et al., 2005) based on guidelines.

Several multifaceted interventions combining patient or parent information leaflets, media campaigns, professional face-to-face or small-group education, and prescriber feedback have been published. In the Netherlands, where antibiotics are used very restrictively, Welschen et al. (Welschen et al., 2004b) managed to decrease prescribing for acute respiratory symptoms by 4% with a multiple intervention, while prescribing increased by 8% in a control group. In a Belgian study (Coenen et al., 2004) a more prominent decrease in the prescribing of antibiotics for patients with acute cough (15.6%, difference to a control group

6.5%) was obtained by a tailored, face-to-face intervention. Three studies from the USA (Gonzales et al., 1999, Perz et al., 2002, Rubin et al., 2005) have shown even grater changes in prescribing practices: a 26% reduction in antibiotic prescribing for adult uncomplicated bronchitis (Gonzales), an 11% intervention-attributable decline in prescribing antibiotics to children aged under 15 (Perz) and a 15.6% decrease in prescribing for URTI, 56% in prescribing for bronchitis and 13.4% decrease in the use of macrolides (Rubin). In rural Alaska, antibiotic courses per person decreased by 31–35% after a multidimensional educational intervention (Hennessy et al., 2002). In South Australia, dispensing volume (in DDD/1000population/day) of the six antibacterials most commonly prescribed for URTIs decreased 32% after a multidimensional campaign focused on public and GPs (Dollman et al., 2005). In Canada an intervention reduced prescribing by 10% while study physicians were also 29% less likely to prescribe second-line antibiotics (Stewart et al., 2000).

Only a few studies have followed the long-term effects of an educational intervention on antibiotic use (Munck et al., 1999, Zwar et al., 2002). These studies imply that in a three- to five-year follow-up, the change induced by the intervention has continued increasing without any further intervention and extended to the control group as well.

In conclusion, it seems that most interventions are effective under some circumstances but none is effective under all circumstances. Interventions based on the assessment of potential barriers as well as multifaceted interventions targeting different barriers to change are more likely to be effective than single interventions.

Antibiotic policy in Finland

Until the end of the 1980s antibiotic policy in Finland was based mainly on the guidance of national and local opinion leaders. Systematic surveillance and reporting of the sales of antimicrobials was started in 1976 (Westerholm et al., 1979). There are several laws regulating the different issues involved in antibiotic policy. A brief summary of the national legislation is presented in Table 4. Finnish legislation is harmonised with the corresponding acts in the European Union. There is no legislation that would obligate the surveillance of infection-specific antibiotic use or resistance in common respiratory pathogens.

In 1993 the National Agency for Medicines gathered together a group of experts from other organisations to act as the 'Antimicrobial Working Group' (Mikrobilääketyöryhmä). The main task of the group was to assess the applications of issuing and renewal of marketing authorisations for antimicrobials, but also to plan antimicrobial policy. With the growing threat of bacterial resistance to antimicrobials since the beginning of the 1990s, it became increasingly important to find ways to get a more detailed picture on the national bacterial resistance trends as well as on the use of antimicrobials as a basis for concrete antibiotic policy.

Table 4.   A brief summary of the key tasks, responsible quarter and regulating acts involved in antibiotic policy in Finland

Task	Responsible	Law
Prevention, diagnosing, treatment, rehabilitation of communicable diseases		
supervision	Ministry of Social Affairs and Health	Communicable Diseases Act Primary Health Care Act
organising	Municipalities	
Infectious diseases register Register of multiresistant bacteria	National Public Health Institute	Communicable Diseases Act
Surveillance of drug sales Drug information Issuing and renewal of marketing authorisations Surveillance of drug marketing Surveillance of clinical trials on medicines	National Agency for Medicines	Medicines Act
Surveillance of certain communicable diseases in animals	Ministry of Agriculture and Forestry	Veterinary Diseases Act
Drug control in veterinary medicine and growth promotion		Medicines Act Veterinary Medication Act The Veterinary Surgeons Act
Use of feed additives	Plant Production Inspection Centre	Feeds Act

The Antimicrobial Working Group launched the idea of the MIKSTRA programme in 1994 (Palva et al., 1994). The main goal of the programme would be to preserve the effectiveness of existing antimicrobials as long as possible, while ensuring patient safety. The activities were to focus on four main targets: continuing medical education of health care professionals, surveillance of the consumption and use of antimicrobials, surveillance of bacterial resistance and information for the public. By coincidence, at the same time the writer of this thesis was becoming interested in the differences in antibiotic use in the Nordic countries and contacted the members of the board to study more about the issue.

The initial activities involved two large meetings around the subject of antibiotics. A medical conference was arranged in autumn 1995 on the use of

antimicrobials in outpatient care. Another, large consensus conference 'Antibiotic resistance - Will medicines remain effective?' was arranged by the Finnish Medical Society Duodecim and the Academy of Finland in November 1997 to outline the future tasks in antibiotic policy and resulting in a consensus statement (Consensus statement, 1997).

It was soon realized that to be able to improve the quality of antimicrobial prescribing, information was needed on which indications each antimicrobial was actually used for in primary care and what were the prescribing rates for each infection. The existing information was fragmented, either infection specific and based on clinical trials done mostly in secondary care or coming from restricted settings, and could not be generalised to antibacterial consumption as a whole. In 1997, representatives of the National Public Health Institute, the Social Insurance Institution, the National Agency for Medicines, the National Research and Development Centre for Welfare and Health (STAKES), the Finnish Office for Health Technology Assessment (FinOHTA) and the Finnish Medical Society Duodecim joined forces to fill this information gap, and start a practical five-year programme named MIKSTRA.

MIKSTRA programme

MIKSTRA (Mikrobilääkehoidon Strategiat–Antimicrobial Treatment Strategies) programme, launched in 1998 is a joint research and development programme, which was designed to optimise diagnostic and treatment practices of common infections in primary care. Particular attention was paid to the evaluation of indication based diagnostic and treatment practices of infections as well as to testing and evaluating different means for guideline implementation. Infection-specific evidence-based clinical guidelines for the MIKSTRA programme were drawn up in collaboration with the Current Care (CC) -programme. In 1999/2000, new guidelines for the six most common infections in primary care were published nationally in the medical journal Duodecim and in the Internet (www.duodecin.fi/kh). A network of 30 health centres was enrolled in 1998 to act as censors of the antibiotic use in the country. The design and practice of MIKSTRA are described in more detail in the methods part of this thesis.

FiRe

Finnish Study Group for Antimicrobial Resistance (FiRe) was founded in 1992 to standardise the methodologies for testing antimicrobial susceptibility in the country to enable national surveillance of the bacterial resistance. FiRe is a coalition of the Finnish clinical microbiology laboratories and the bacteriology units of the National Public Health Institute (www.ktl.fi/extras/fire). Today all the clinical microbiology laboratories in the country participate in FiRe and have adopted a common FiRe method as a standard for their diagnostic routine.

FiRe's primary task is to produce reliable and comparable information on the antimicrobial resistance among pathogenic bacteria isolated from the clinical specimens submitted to the laboratories, both from hospitals and health care centres in Finland. The comparability of the results obtained and the proper performance of the FiRe laboratories are surveyed on a regular basis. The susceptibility data produced by the laboratories is collected annually for an internet-report and delivered also for use to the European Antimicrobial Resistance Surveillance System, EARSS.

Treatment recommendations

When the increase of information in medicine was not yet as fast as it is today recommendations given in medical journals and textbooks updated at a five- to ten-year interval were sufficient. In addition to these, the Finnish National Board of Health started to publish a national recommendation booklet -series 'Kapseli' at the beginning of the 1970s on selected items. Later the National Agency for Medicines continued this practice together with the Social Insurance Institution, which continues until today. In 1981 the first booklet on antimicrobial treatment in this series was published (Valtonen & Makkonen, 1981) and a completely revised version was published at the end of 1995 (Huovinen & Vaara, 1995). The medical industry had also published recommendation booklets of their own since the 1970s (and still does), written by national experts and opinion leaders (Peltola, 1996).

Evidence-based management guidelines (Current Care programme)

The rapidly increasing information and the number of guidelines of varying quality has given rise to a need to develop national, evidence-based clinical practice guidelines for the Finnish health care system. This led to the start of the Current Care (CC) programme, in the Finnish Medical Society Duodecim, as a component of the national health strategy. The CC-programme is supported by the Finnish Ministry of Social Affairs and Health and by hospital districts.

In practice, developing a new guideline starts when the board of Current Care select a topic for the Current Care guideline from among suggestions made mostly by specialist societies. The guidelines are produced by expert panels representing all relevant clinical specialties in the field in question, including always a general practitioner. The process begins with a literature search done by an experienced medical librarian. The following step is the critical appraisal of the literature, based on criteria originally outlined by the Evidence Based Medicine Working Group. The level of evidence is graded from A to D. Prior to publishing all guidelines are exposed to a wide review process. CC-guidelines are also updated on a regular basis.

48

All Current Care guidelines are published in the medical journal Duodecim and are freely available on the Internet (www.duodecin.fi/kh). Electronic versions are also available on CD-ROM. The electronic versions also give access to the evidence summaries on which the grading is based and direct links to the original Cochrane reviews. The electronic version is the main medium of guideline dissemination.

The first published Current Care -guideline appeared in 1997 on celiac disease. CC-guidelines on common infections in outpatient care were among the first wave of guidelines. Today there are 63 guidelines all-together that have appeared about different fields of medicine.

ROHTO

From the beginning of 2004, an independent unit was set-up by the Ministry of Social Affairs and Health in administrative connection with the National Agency of Medicines to promote rational pharmacotherapy. For this purpose, ROHTO evaluates and disseminates information on evidence-based pharmacotherapy, implements knowledge to promote more rational pharmacotherapy, monitors, describes and studies prescription practices, conveys benchmarking data to prescribers, and supports the development of electronic decision-support systems. The prescribers particularly in primary health care are the focus of activities.

The dissemination and implementation of knowledge is based on local ROHTO educational and development activities co-ordinated by regional facilitators in hospital districts and by local facilitators in primary care health centres. The facilitators are experienced GPs, but active support by the management of hospital districts and health centres is essential. ROHTO activities are based on participatory methods, scientific evidence, and producer-independent information on drugs. The decision on which items are discussed in ROHTO activities is done locally. Infections and antibiotics have been selected for topics on several occasions.

The ROHTO-centre evaluates, summarises and disseminates information on evidence-based and cost-effective pharmacotherapy. Dissemination is mainly done via a permanent column of the Finnish Medical Journal and on the ROHTO website. The selection for topics is based on the following main criteria:
- new medicines on the market and their status among the conventional medicines is unclear
- medicines that have been on the market for a few years that are informed by new data on requiring a redefinition in their status, and
- medicines used by large patient groups.

Among others, short reports of the main results of MIKSTRA programme have been reported in this column.

Outlines for the future

In March 1999 the Ministry of Social Affairs and Health set up a Working Group to provide proposals for controlling bacterial resistance and developing antibiotic policy (Bakteerien lääkeresistenssin torjuminen ja mikrobilääkepolitiikan kehittäminen -työryhmä, 2000). The group stated that Finnish legislation is well placed and in line with the European Union recommendations. Finland has started to build up all the essential systems needed for controlling the spread of antimicrobial resistance. Further development was suggested, however, on data collection methods in resistance surveillance, thus allowing an early warning system; on continual updating of treatment guidelines; on improving information collection on the consumption of antimicrobials for each animal species; on education for professionals; on monitoring the attitudes of professionals and the public; and that change in bacterial resistance should be taken into account when issuing and renewing marketing authorisations for antibacterials. The working group suggested that a fixed-term Monitoring Working Group would be appointed to encourage and monitor these activities. Such a group has not been appointed, however. At the moment there is no one body in Finland that has responsibility or a mandate to co-ordinate the antibiotic policy activities that are ongoing within different organisations.

AIMS OF THE STUDY

At the beginning of 1990s alarming reports on increasing bacterial resistance to common antibiotics were emerging from all over the Western world. It is known on the basis of sales registers, that most antibiotics are prescribed in outpatient care. It is not evident however how antibiotics are used in different infections, as such data is not available in any registers. There is also a need for evidence-based treatment guidelines for common infections in outpatient care. To be able to make and implement guidelines effectively, detailed information of the diagnostic and treatment practices of infections in outpatient care would be needed. The aim of this study is to yield such information to provide a basis for future antibiotic policy.

The specific aims of this study are

1. To develop a method to survey the management of infection patients in outpatient care and to test the feasibility of the method and the representativeness of the obtained result (I).

2. To study the prevalence of infection diagnoses in primary care to identify which infections are the most important ones from the point of view of the total use of antibiotics (I, II)

3. To study if diagnostic aids are used adequately to achieve correct infection diagnosis (III)

4. To study if antibiotic prescribing can be changed by implementing national treatment guidelines by means of continuing medical education at the work site (IV)

-

MATERIAL AND METHODS

This thesis is based on results acquired from
- a prospective, multi-centre prescription study in Pirkanmaa hospital district in 1994 (I),
- a prospective, multi-centre prescription study in a national MIKSTRA network of 30 health centres in 1998 (II, III), and
- a prospective, before-and-after intervention-study in the MIKSTRA network of 30 health centres (1998–2002) and in 20 control health centres (2002) (IV), as well as
- unpublished observations acquired from a patient questionnaire study within the MIKSTRA study and an external evaluation of the MIKSTRA training intervention.

This thesis describes the broad context of the surveillance of infection-specific antibiotic prescribing and the main results of the educational intervention aimed at improving the quality of prescription. The obtained data gives possibilities for a further analysing of the more detailed aspects of the topics that have been highlighted here.

Recruitment and Study population

Pirkanmaa study (I)

In 1994, Pirkanmaa Hospital District in southern Finland had a population of 436 000, which was 9% of the entire population of the country at that time. The demography of the area was similar to the average in Finland. Primary health care services were provided by 35 municipalities at 20 health centres with 237 general practitioner posts in total. According to the Finnish national prescription register the crude pattern of antibiotic use in Pirkanmaa approximated very closely to the mean pattern in Finland in 1994 (Figure 8). The area was considered to be a good example of the whole country and estimated to be big enough to give sufficient information on antibiotic use in primary care from one week of data collecting.

The chief medical officers of all 20 health centres were sent an invitation by letter for their health centre to participate in a one-week data collection. The

main researcher and the local infection specialist participated in the chief medical officer's bi-annual meeting to explain the study details. All health centres agreed to participate. The main researcher familiarised the chief-medical officers with the practical arrangements at a further meeting before the locally organised data-collection took place.

Figure 8. *Antibacterials for systemic use (J01), distribution of consumption (DDD/1000 inhabitants/day) in the whole Finland and in Pirkanmaa Hospital District in 1994 (Source: National prescription register)*
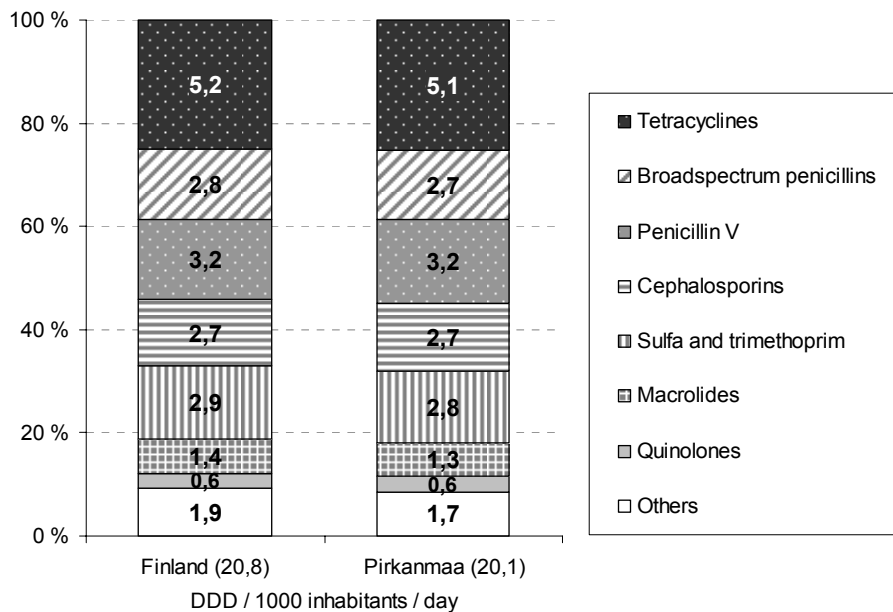
MIKSTRA study (II-IV)

In March 1998 a letter was sent to all Finnish health centres (N=256) asking whether they would participate in a five-year study with the objective of changing the management of common infections towards a more evidence-based practice. In addition, an open invitation for participation was published in the Finnish Medical Journal (Suomen Lääkärilehti) (Lauslahti et al., 1998). The 82 health centres that expressed a willingness to participate were sent a questionnaire asking basic information concerning the health centre. The main topics in the questionnaire are presented in Table 5 and the whole questionnaire (in Finnish) is in Appendixes/Questionnaires.

Based on the background information received from the health centres and national statistics, 30 health centres were enrolled representing roughly the

54

whole country with respect to type (rural/urban), size, geographical location (Figure 9), and antibiotic sales from the pharmacies in the area.

Table 5.   The main topics in the questionnaire on background information for the candidate health centres

1.	Name of the health centre
2.	Name and contact information of a possible local contact person
3.	Population at the end of 1997
4.	Distance to nearest hospitals
5.	Number of health stations
6.	Number of doctors
7.	Have certain infection patients been delegated to nurses?
8.	How are on-call services arranged?
9.	Availability of certain diagnostic aids or tests
10.	Has the health centre computerised patient records?
11.	Microbiological reference laboratory
12.	Who will sign the official contract on behalf of the health centre?

Figure 9.   *Geographical distribution of MIKSTRA study and control health centres*
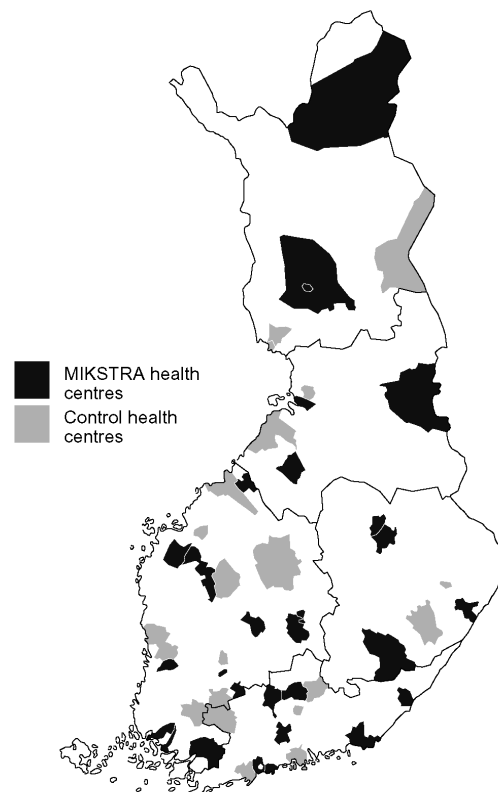
The questionnaire on background information was repeated after final data-collection in 2002. When the MIKSTRA-programme started in 1998 there was still an oversupply of doctors in the labour market following the economic depression in the beginning of 1990s. As all GP posts were still filled in 1997 (Vehkasaari, 2002), this was not specifically asked when collecting the basic information of the health centres in 1998. While repeating the questionnaire on basic-information for the health centres in 2002, however, questions regarding any change or shortage of personnel were included (Appendixes/Questionnaires in Finnish).

The population covered by the study group health centres was 819 777 (16% of the Finnish population), with some 460 health centre physicians among the personnel. The two health stations of the city of Helsinki (Alppiharju and Latokartano, later called Pihlajamäki-Viikki) were regarded as independent health centres. Although their population-base was less than 50 000, they were representatives of a large city, as were the health stations of the city of Espoo (Tapiola as a MIKSTRA health centre and Viherlaakso as a control health centre). The details of the key characteristics used in selection of MIKSTRA study health centres are presented in Appendixes/Table 2.

None of the health centres dropped out during the study period. However, one medium-sized health centre (Mäntsälä) did not participate in the 2001 data collection. Further, due to the re-organization of health care services in two big cities, two health stations that provide on-call services within them withdrew from the study in 1999 (Turku) and 2000 (Oulu) respectively. All other health stations within these cities participated normally in all of the data-collecting.

Another 30 health centres – already potential candidates for the study group in 1998 but not included then – were invited in spring 2002 to participate as control health centres for a single week-long episode of data collection. Twenty of them agreed, covering a population of 545 098 and employing roughly 345 physicians during that week period (374 GP posts of which 29 were not occupied). The details of the key characteristics used in selection of control health centres are presented in Appendixes/Table 3.

Available resources limited the number of health centres that can be recruited. Therefore the study health centres represented the whole country only roughly considering all aspects. As ten of the original 30 selected control health centres had to withdraw at a late stage of process (such that they could not be replaced), because of the shortage of doctors, the control group ended up being somewhat biased in respect of prescribing (less consumption of antibiotics in the area) compared to the MIKSTRA study health centres, and geographically not totally representative of the whole country (Figure 9, Table 6). Further, the control group was not well balanced with the study group in respect of proportion of big cities as the originally interested two health stations from the city of Helsinki cancelled their participation and three other invited big cities were not willing to participate either.

Table 6. Comparison of the characteristics of MIKSTRA study health centres, control centres and the whole population of Finland

	MIKSTRA health centres		Control health centres		National	
	Health centres N (%)	Population N (%)	Health centres N (%)	Population N (%)	Health centres N (%)	Population N (%)
Population (1997)						
<10 000 (Small)	8 (28)	55 785 (7)	5 (25)	39 164 (7)	125 (49)	0.77 million (15)
10–50 000 (Medium)	15 (51)	337 871 (41)	12 (60)	300 588 (55)	115 (45)	2.42 million (47)
>50 000 (Large)	6* (21)	426 121 (52)	3 (15)	205 346 (38)	16 (6)	1.96 million (38)
Total (% of national)	29* (11)	819 777 (16)	20 (8)	545 098 (11)	256	5.15 million
Type (1997)						
Rural	15 (50)	163 469 (20)	10 (50)	125 153 (23)		
R/U**	9 (30)	230 187 (28)	6 (30)	189 663 (35)		
Urban	6 (20)	426 121 (52)	4 (20)	230 282 (42)		
Antibiotic prescriptions /1000 inh. (1996)***						
<500	9 (30)	181 480 (22)	8 (40)	181 514 (33)	82 (32)	1.28 million (25)
500–600	10 (33)	270 662 (33)	7 (35)	173 088 (36)	94 (37)	1.64 million (32)
>600	11 (37)	367 635 (45)	5 (25)	169 524 (31)	80 (31)	2.23 million (43)

*Two health stations of Helsinki counted here as one

**R/U: health centres formed by an urban city with surrounding small rural municipalities or of smaller municipalities contiguous to big cities

*** Source: National prescription register

Data collection

Pirkanmaa study (I)

In November 1994, all doctors at the 20 health centres in Pirkanmaa were asked to fill in a case-report form during a one week period (week 46 - from Monday 8.00 am to Monday 8.00 am) for each patient consultation related to an infection. Patients consulting by telephone were also included, but elderly patients living in nursing homes or in the health centre ward were excluded. The forms were to be completed irrespective of whether the patient was prescribed an antibiotic or not. Only one diagnosis (the main diagnosis) per form was to be given and only antibiotics for oral, systemic use were included. However, five reported cases of parenteral treatment (three cases of erysipelas and two of pneumonia; 0.2% of all antibiotic treatments), were also included. The choice of antibiotic, dose and package size, were recorded in the same way as in a prescription. The main topics of the single page (A4 size) case-report form are presented in Table 7 and the complete form is included is Appendixes/Questionnaires (in Finnish and in English). Infections were classified into 14 categories, including seven categories for respiratory tract infections. A category for infection prophylaxis and no infection were also included in the choices. So as not to interfere with physicians' prescription habits, diagnostic criteria were not standardized but doctors used the criteria they were accustomed to in their daily work. The prescribing doctors were asked to sign the case-report form with their personal professional identification code, given by the Social Insurance Institute, and also the stamp of the health centre.

Self-estimations of the reliability of the diagnosis, the anticipated benefit of the antibiotic and also the doctor's perception of the patient expectations on receiving antibiotics were indicated by making a tick on a visual analogue scale of 1–5, with opposing statements at each end of the scale. The case-report form was pre-tested in actual prescribing situations. The chief medical officers of the health centres organized the collection of the completed case-report forms at the end of the study-week and their collective mailing to the researcher.

One month after the indication survey, doctors in the health centres in Pirkanmaa were sent a separate questionnaire regarding sources of information about and attitudes on antimicrobials (data not presented). This questionnaire also included, however, a question on whether the doctor had participated in the previous prescription study and a request to estimate the proportion of his or her infection patients for which he/she had completed the case-report form for during the study week.

58

Table 7.   Topics included in the case-report forms of the Pirkanmaa study and the MIKSTRA study

---

Questions included in both study forms

1. Sex and year of birth of the patient
2. Type of consultation (scheduled or home visit, out-of-hour visit, telephone consultation)
3. Main diagnosis
4. Duration of symptoms, in days (classified into four categories)
5. Treatment with antibiotic (yes/no, had already)
6. Patient's expectations on antibiotic prescription (demanded–resisted, scale 1-5)
7. Prescribed antibiotic, strength, dose and package
8. Doctor's signature and stamp of the health centre

Questions included in Pirkanmaa study only

9. How certain is the doctor of the diagnosis (scale 1-5)
10. How probable does the doctor regard the benefit of antibiotic in that specific case (scale 1-5)
11. New antibiotic treatment or change/continuation of previously started treatment

---

Questions included in MIKSTRA study only

9. Patient's smoking (yes/no, how much)*
10. Scheduled control visit (yes/missing)**
11. Diagnostic procedures (14 options including 'non' and 'other', with a definition which)
12. Referrals and consultations (six options including 'no')
13. Sick leave or parental-leave (yes/no, for how many days)
14. Factors influencing the choice of antibiotic treatment***
15. Prescribed or recommended symptomatic medication
16. First or re-consultation for the infection episode (how many consultations in all)
17. New appointment (yes/no/if needed/by telephone)**
18. Participation on MIKSTRA-training****

---

*from year 2000 onwards only
**from year 1999 onwards only
***four choices in 1998; six including 'other', with a definition which, from
    1999 onwards only
****in 2001 and 2002 only

MIKSTRA study (II-IV)

After the Pirkanmaa study, it became obvious that data on the management of outpatient infections was needed from the whole country. At the same time preparations were made for producing new Current Care -guidelines for the most common outpatient infections. Thus, the MIKSTRA study was also used in implementing and evaluating the effect of these guidelines. Although nurses are not allowed to prescribe medicines in Finland, they are allowed to give short sick leaves. As it seemed that an increasing number of patients in health centres were primarily referred to nurses, it was decided that the data-collection in MIKSTRA study would be expanded to include nurses as-well.

Each year from 1998 to 2002 during one calendar week in November (week 46), the physicians and nurses in the study health centres and (in 2002 only) the control health centres, filled in a structured case-report form on every patient that had a consultation for an infection. The case-report form was a modification of the one used in the Pirkanmaa study. Some of the previous items were left away and some new items were included (Table 10). Since the results of the possible diagnostic tests were in many cases not available during the same consultation-visit, it was not requested that they be recorded in the case report forms. One of the added items was factors influencing the decision of antibiotic choice. This included categories of allergy, other previous side effect/s, pregnancy or weaning and patients wish, and from 1999 onwards also chronic or relapsing infection and 'other', with a 'please specify'. Symptomatic medication was recorded in a similar way as antibiotics except that instead of package size, only the duration of treatment was given. The case-report forms for the MIKSTRA data-collection in 1998 and 2002 are presented in Appendixes/Questionnaires (in Finnish and in English).

The patients were also asked to fill in a questionnaire while waiting for their consultation (questionnaire available at www.mikstra.fi). Patients were asked about the main reasons for the consultation, symptoms and their duration and severity, as well as patient's expectations towards the consultation and treatment. A random sample of patients with otitis media, sinusitis, tonsillitis, acute bronchitis, unspecified URTI, skin infection or UTI - approximately 200 patients per each infection group annually - were telephoned 10–14 days after the consultation. In the telephone interview patients were asked about their recovery, possible hospitalisations and re-consultations necessitated by the illness. Some unpublished items of these data have been used in this thesis.

Intervention (IV)

Evidence-based treatment guidelines were drawn up by the Current Care Program of the Finnish Medical Society Duodecim, on the six most common infections in outpatient care. Guidelines for acute otitis media, acute sinusitis,

throat infection, acute bronchitis and bacterial skin-infections were published in October 1999 (Blomgren et al., 2005, Honkanen et al., 1999, Puhakka et al., 1999, Ranki et al., 1999, Sarkkinen et al., 1999), and likewise for urinary tract infections (UTI) in March 2000 (Ikäheimo et al., 2000). The guidelines were used as teaching material. Additional educational tools, including case histories, PowerPoint presentations, patient leaflets and posters, were produced for the study group health centres by the MIKSTRA research group.

The educational intervention focused on training one physician from each health centre in the study group to be a trainer at his/her work site. The training of trainers comprised two half-day orientation seminars in 1999, two 2-day seminars on training methods in 2000 and 2001, and three half-day sessions on guidelines in small groups in 1999-2001. The trainees and the research group also had a joint meeting once a year before the data-collection week. Feedback on the results of previous data collections was given in each training session and in meetings. Articles on selected topics, based on results of previous data collections, were published in the Finnish Medical Journal in the week before data collection, and presented to media in press conferences.

After collecting baseline information in November 1998 the study group health centres could start implementing the guidelines. Half of the health centres (the group-A health centres) started the first study period (from October 1999 to October 2000) by implementing the guidelines of otitis media, throat infection and UTI, and the other half (the group-B health centres) started with acute bronchitis, sinusitis and skin infections. In the data-collections of 1999 and 2000 the two groups were to serve as controls to each other. After the data-collection in 2000 the health centres were instructed to start implementing the other set of three guidelines during the second period (from December 2000 to October 2001). The local training utilized interactive methods, problem-based learning (PBL) or academic detailing (AD), and group discussions with case histories. The process was followed by questionnaires and a telephone interview performed by the trainer of trainers in summer 2000. An external researcher afterwards evaluated the realization of the intervention and the experiences of the GP trainers by means of surveys and telephone interviews.

Data processing and statistical methods

Pirkanmaa study (I)

The collected case-report forms were sent from the health centres to the researcher, who coded all recorded antibiotic preparations for data entry. The code included information on the brand-name, strength and mode of preparation.

The data was saved in Excel-form for check-up and correction of mistakes made in data entry. Frequencies and cross-tabulation was used to look for inconsistencies and where such were found the original case-report form was cross-referenced. The diagnosis group *'Other infection, please specify?'* (n = 184) was checked and when necessary reclassified, e.g. abscesses and infected wounds classified to this group were reclassified as *'Skin-/wound infection'* and *laryngitis and tracheitis as 'Bronchitis'*.

SAS® software was used to perform the statistical analyses. Cross-tabulation and percentages were used to describe the occurrence of each outcome. Logistic regression analysis and F-test were used for testing the significance of patient expectations.

MIKSTRA study (II-IV)

Named, local contact-persons (often the same person as the health centre trainer) collected the completed case-report forms and patient questionnaires and sent them to the main researcher (UMR). Prescriptions of antibiotics were coded before data entry in a similar way as in the Pirkanmaa study. Symptomatic medication was coded for data entry as well, but the code was simpler, including only the brand-name and mode of preparation. The diagnostic procedures, which did not fit in the given codes but were given in the category *'Other, please specify'* were coded before data entry as well. Before starting analyses all data were checked using frequency tables and cross-tabulation and in case of any inconsistencies the original case-report forms were referred to and data corrected if falsely entered.

Missing information was in most cases regarded simply as missing. Antibiotic prescription was elicited in two ways, by a question 'did you prescribe antibiotic (yes/no/had already)' and by asking for a definition of the substance. If information was missing from both of these two questions it was interpreted to be 'no'.

Paper II

Cross-tabulation and percentages were used to describe each outcome. All patients in the 1998 data-collection, except those who eventually did not have infection, were included in the analysis. The data were processed using Excel and SAS® software

Paper III

In this study, only first consultations for a respiratory tract infection in 1998 data-collection were included. The data were processed using SPSS® for Windows software and the chi square test was used to test for significance.

Paper IV

In this study all patients with infection and all study years were included. The main outcome measures in assessing the success of the guideline implementation were the concordance of prescribing with the guidelines in respect of selecting first-line antibiotic choice when prescribing at first consultation for the infection episode and prescribing for the recommended duration of treatment. Secondary outcome measures were the proportion of patients who were prescribed antibiotics by indication and also the use of relevant diagnostic tests.

When studying the change in the study group health centres, 2001 (first year after intervention) was compared to 1998 (before intervention). Data from 2002 (follow-up) was used when comparing the study group health centres with the control health centres. In the statistical analysis, percentages were used to describe the occurrence of each outcome. Odds ratios (OR) with 95% confidence intervals (CI) as well as P-values for ORs were used to measure the change in each situation. Because of the multi-centre study setting, a mixed effects model with the health centre as a random effect was used when calculating the ORs for the selection of first-line drug and for the compliance with recommendations on the duration of antibiotic treatment.

The overall concordance of prescribing for respiratory tract infections with that recommended was analyzed using a chi square test. We defined antibiotic prescription for respiratory tract infections as 'correct' in the following situations: prescribing the recommended first-line antibiotic for the recommended duration for acute otitis media, sinusitis or streptococcal tonsillitis or other than the first choice antibiotic for these infections in cases where the treatment decision was justified by allergy or other previously observed side-effect. Pregnancy or weaning was not an acceptable justification for deviation from the recommended because all first-line recommended antibiotics for RTIs are permitted in these conditions, nor did we accept patient's expectation as a sufficient justification. From the 1999 data collection onwards, other justifications were also asked (including preceding antibiotic treatment, chronic or relapsing or prolonged infection, or other, including immunocompromised patient, test-results or other epidemiologic information). As these justifications were not asked in the baseline data collection in 1998, they we not used in the main analysis. Because pneumonia and infection-related exacerbation of chronic lung diseases were not included in the infections undergoing intervention, use of any antibiotics for these infections is presented separately.

All analyses were made on an intention-to-treat basis. The data were processed using SPSS® software version 12 and SAS® version 8 and macro GLIMMIX (General Linear Model for Mixture Distributions), which is a procedure that fits statistical models to data with internal correlation or nonconstant variability, and where the response is not normally distributed.

Ethical considerations

The MIKSTRA study protocol was approved by the Ethics committee of the Hospital District of Helsinki in November 1998. During the data-collection period, when an infection related patient entered the study health centre, he or she was told that the health centre is participating in a study and he/she was asked to participate by filling in a questionnaire while waiting for the health professional. The patient-questionnaire included written information about the study and a signed consent form for the telephone interview (available at www.mikstra.fi). The questionnaire completed by the patient and the case-report forms completed by the health professional and the telephone interviewer were linked together with a common identification code. No personal identification of the patients other than sex, year of birth and health centre was entered into the final database.

For public health reasons it was regarded as unethical to delay publishing nationally both the new evidence-based treatment guidelines and the results of the MIKSTRA study, even though there was awareness that it may contaminate the control group.

RESULTS

Feasibility of the method and representativeness of the data

Pirkanmaa study (I)

In the Pirkanmaa study, a total of 4150 consultations for an infection were recorded by 223 doctors during the study week in the twenty health centres of the Pirkanmaa hospital district. No official source was available to assess the total amount of patients with infection during the study week. However, a participation rate of 223 doctors per 237 GP posts in the area is very high (94%) and indicates good compliance.

One month after the prescription study, a questionnaire for the practicing doctors in the same health centres was sent out and 275 doctors completed it including temporary substitutes and chief medical officers. Three quarters of the respondents (207 doctors) reported that they had participated in the prescription study. Of them, 205 doctors answered the request to estimate the proportion of their patients having infection for which they had filled the case-report form during the prescription study week. The mean estimation was that they had filled the form for 89% of their infection patients. This implies a good coverage and representativeness for the data obtained.

In the prior test of the study case-report form, completion of one case-report required on average 20 seconds if no antibiotic was prescribed, and 40 seconds if the patient received medicine. Of the doctors participating in the study, 95% completed $\leq$ 40 case-report forms during the study week (average 18.6/doctor). As the estimated mean time needed to fill one case-report form was 33 seconds this means that 95% of doctors used 22 minutes per week at the most or an average of 4.4 minutes per working day to fill in the forms. This amount of extra work seems reasonable and was probably supportive to the compliance.

The hospital district had asked the health centres of Pirkanmaa to count all their out-of-hour visits during the very same week that our data collection took place. We also received this data from the health centres and used it to calculate that 37% of all out-of-hour visits during the week were due to infections.

MIKSTRA study (II-IV)

The case-report form used in the Pirkanmaa study was modified for the MIKSTRA study. Some questions were added and thus the average time needed for completion of one case-report form was raised to one minute. The participation rate of the doctors remained very high, however.

The population base of the study health centres increased by some 20 500 inhabitants (3%) from 1998 to 2002 and the number of GP posts increased by at least 41 (9%), but the actual number of GPs at work during the study weeks were roughly the same in 1998 and 2002 (Table 9). Even as much as one quarter of the GP posts were unoccupied in some of the study health centres in 2002, while the average deficit of doctors was 8%. Furthermore, the 20 health centres who had the data available reported that 40% of their doctors had left since 1998 and 24 health centres reported that 18% of their GP posts were hosted by temporary substitutes in 2002. This significant turnover among personnel probably explains why only one fifth of all the 953 doctors who participated in the data collection in the MIKSTRA health centres during the five study years, participated in more than three data collections and half of all doctors participated only once (Table 8).

If the number of GP posts in 1998 (459) is used as the comparison, the participation rate in MIKSTRA health centres was 99% in 1998 and 88%, 85%, 81% and 88% in the consecutive years from 1999–2002 respectively. In the control health centres in 2002 there were 374 GP posts of which, according to the reports of the health centres, at least 29 were not occupied during the study week. As 304 doctors participated in the data collection in the control health centres, the participation rate was 88%.

Table 8.   How many times (years) did the doctors participate in MIKSTRA data collection?

No. of data collections	No. of doctors	Per cent	Cumulative per cent
5	86	9,0	9,0
4	101	10,6	19,6
3	135	14.2	33,8
2	156	16,4	50,2
1	475	49,8	100
Total number of participating doctors during five study years	953	100	

Table 9. Population change from 1998 to 2002, number of GP posts in 1998 and 2002 and number (%) of GP posts occupied in 2002 at MIKSTRA study health centres

Health Centre	Population change from 1998 to 2002	No. of GP posts 1998	No. of GP posts 2002	No. (%) of GP posts occupied during study week 2002
Asikkala	-141	6	6	6 (100)
Espoo, Tapiola	-203	15	17	17 (100)
Haapavesi	975	6	7	7 (100)
Hamina+	-1 171	15	13	10 (77)
Hki, Alppiharju	0*	7	7*	7*
Hki, Latokartano	0*	6	6	5 (83)
Inari	-490	6	7	7 (100)
Joutseno	-549	6	6	5 (83)
Juva+	-1 244	9	9	7 (78)
Jyväskylä	4 816	46	56	53 (95)
Kannus	-250	4	4	3 (75)
Korpilahti+	681	8	9	9 (100)
Kyrönmaa+	-607	12	12	11 (92)
Lammi+	-113	5	5*	5*
Masku+	927	7	7*	7*
Mäntsälä	1 515	8	10	10 (100)
Mänttä+	-3 995	11	18	15 (83)
Nilsiä	-1 121	6	7	5 (71)
Oulu	11 252	60	60*	60*
Pirkkala	1 847	8	11	11 (100)
Rovaniemi city	567	23	25	22 (88)
Rovaniemi rural	-225	12	11	10 (91)
Salo+	1 715	29	34	30 (88)
Seinäjoki+	2 771	30	36	36 (100)
Suomussalmi	-1 121	6	7	5 (71)
Tormajärvi+	-1 055	4	4	4 (100)
Turku	6 925	79	79*	65** (82)
Ulvila+	-527	8	8	7 (88)
Valkeakoski	-264	14	16	16 (100)
Varpaisjärvi	-333	3	3*	3*
All (% occupied)	20 582	459	500	458 (92)
No. of GPs in data		454	405	405
Participation-rate		99%	81%	88%

*data from 2002 not defined; figures from 1998 used

**number of potentially participating doctors in 2002 given by the health centre

The average number of case-report forms completed by each doctor in 1998 was 14.5. The corresponding figures for following years 1999–2002 were 12.7, 12.7, 10.6, and 11.0 respectively and 12.7 for the control health centres in 2002. On average 14% (range 11–20 %) of the case-report forms were filled by nurses. Only 0.3 per cent of the case-report forms were not signed.

The number of recorded prescriptions of antibiotics in the 1998 data-collection (N=3555) was compared to the total amount of antibiotic prescriptions in the national prescription register prescribed by the same doctors during the data collection week. Our data-collection covered on average 73% of all prescriptions (N=4883) prescribed by the 454 doctors identified in both data sets during the study period (unpublished data).

Patients with infections in primary care (I, II, IV)

The age and gender distribution of infection patients differs remarkably from that of the total population of Finland (II, Figure 10). Women comprised about 60% of all patients with infection, both in the Pirkanmaa study and in MIKSTRA, except in the youngest age group of 0–4 years, where male patients were in the majority. The proportion of elderly patients (aged 65 or over) was almost half of their proportion in the population (15%), 8% in Pirkanmaa and 7% in MIKSTRA 1998.

Children less than 15 years of age comprised 36–39% of patients with infection in all data-collections, while they account for 20% in the total population. More than half of the children were less than five years of age. Children were overrepresented in most of the diagnosis groups, but their percentage was especially high in otitis media (84% in Pirkanmaa in 1994 and 82% in MIKSTRA in 1998) and unspecified URTI (49% and 43% respectively) and in respiratory tract infections in general (44% in the Pirkanmaa study).

Figure 10. *Age and gender distribution of infection-patients in MIKSTRA study in 1998–2002 and the whole population of Finland in 2004*

Number of consultations

MIKSTRA study

Population (thousands)
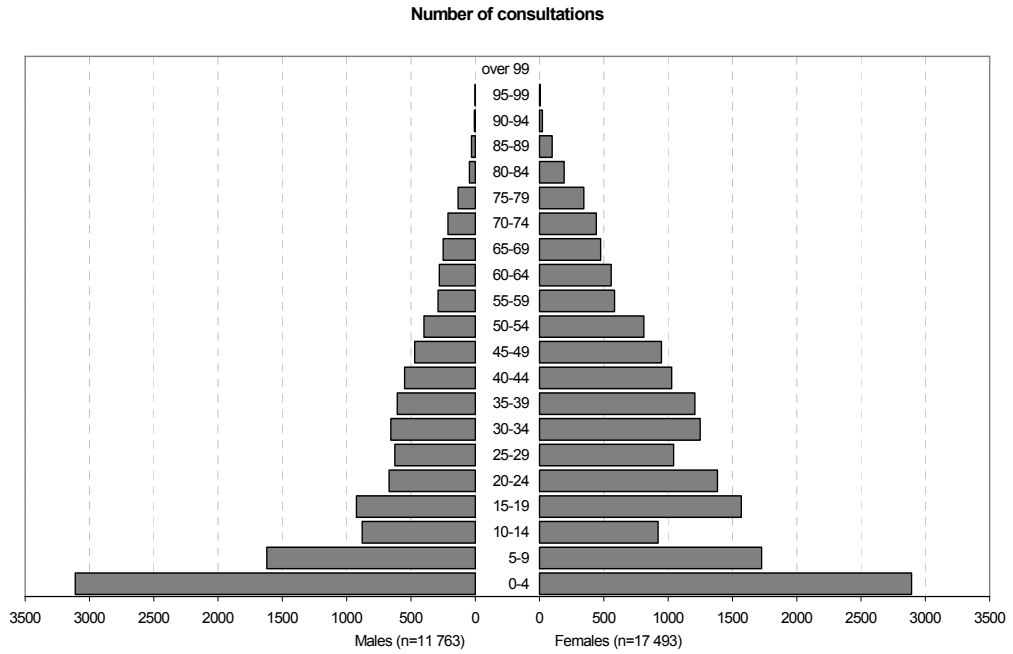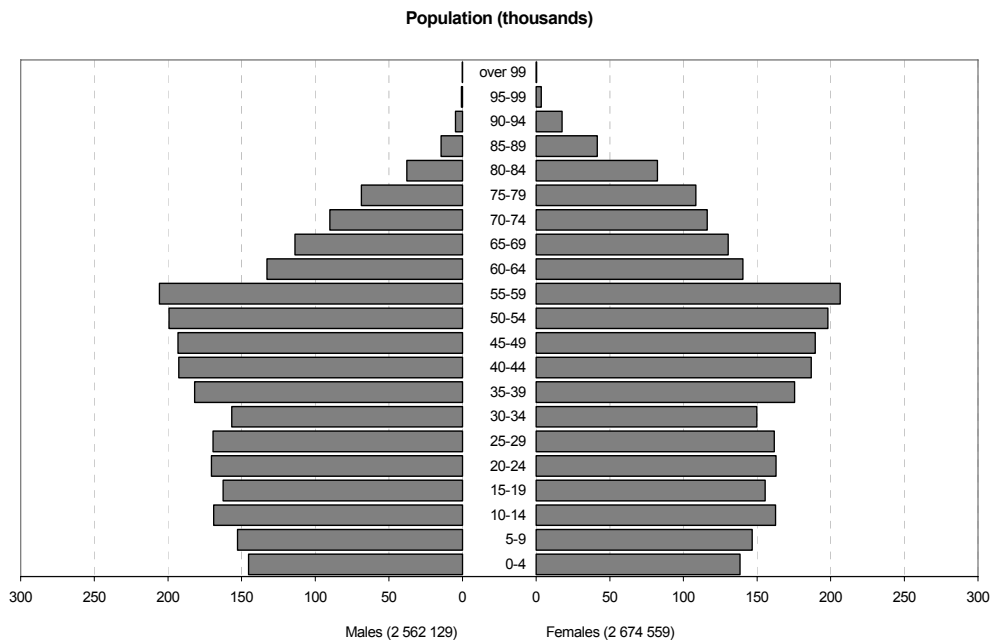
Whole population

Small peaks in the age-distribution of patients with infections are also seen in adolescents aged 16–25 and adults aged 31–41 years, both more prominently in females (Figure 11).

Figure 11. *Age and gender distribution of infection patients in MIKSTRA 1998–2002 by age in years (N=29 043; light: women; dark: men)*
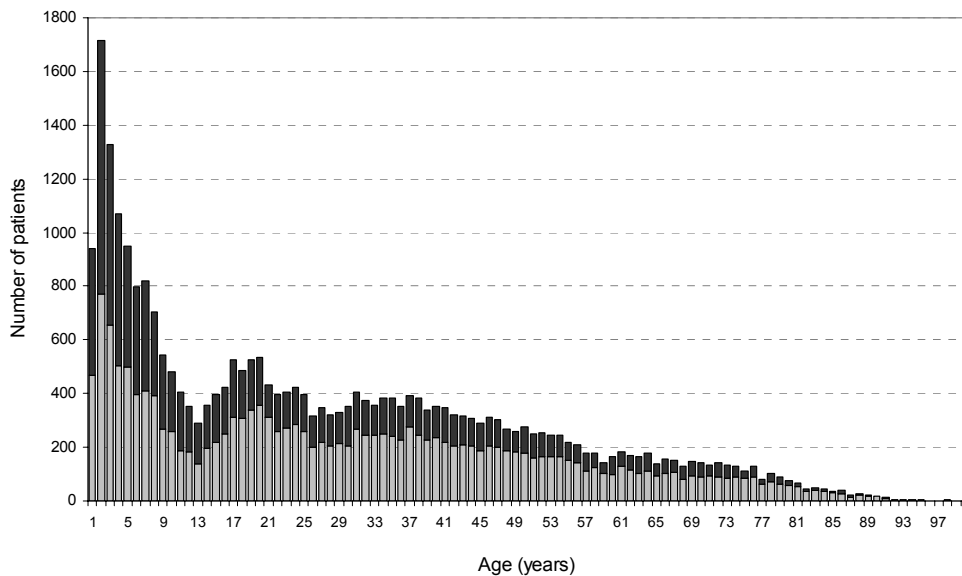
Three quarters of the visits to health centres for an infection were out-of-hours consultations and most of them (81%) were first consultations for the infection episode (II). Re-consultations were, on average, more common among those who had attended a health centre for pneumonia (45%), sinusitis (26%) or otitis media (24%). Two per cent of infection patients were referred to secondary care and the rate was stable over the years (IV).

The distribution of infections in primary care seemed to be fairly stable over the years (I, II and IV) (Table 10). Respiratory tract infections comprised three quarters of all infections with unspecified URTI, otitis media and sinusitis as the most common diagnoses. The only major difference in the distribution of diagnoses seems to be the remarkably higher prevalence of bronchitis in the Pirkanmaa study (14%) compared to the MIKSTRA-data (7–9%).

There was a notable variation in the infection panorama between different age groups of patients (II). Respiratory tract infections comprised 83% of all infections in children under five but only 50% in the oldest age group of > 65 yrs (Figure 12). URTI and otitis media comprised 70% of all infections in the youngest age group of less than five years of age, 50% in the older children (5–14 yrs), 30% in adults and less than 20% in elderly patients. The oldest age group was the only one not to have respiratory tract infections among the two most common diagnoses. Urinary tract infections was the main diagnosis in the patient group of >65 years of age followed by skin infections and sinusitis.

70

**Table 10.** Distribution of diagnoses in Pirkanmaa- and MIKSTRA-studies

Diagnosis	Pirkanmaa	MIKSTRA study and control health centres					
	1994	1998	1999	2000	2001	2002	Controls 2002
	%	%	%	%	%	%	%
Unspecified URTI*	21	25	29	28	27	30	29
Otitis media	16	16	15	15	16	14	12
Tonsillitis	9	8	7	8	5	6	6
Pharyngitis	6	4	3	3	3	3	3
Sinusitis	11	12	12	11	14	12	12
Bronchitis**	14	8	8	8	9	8	7
Pneumonia	2	1	1	2	2	1	1
All respiratory tract infections	79	74	74	74	77	74	70
Skin infections	7	6	5	7	6	6	7
Urinary tract infections	6	6	6	6	5	5	5
Intestinal infections	2	4	3	2	3	6	7
Gynaecological infections and STDs***	2	2	1	1	1	1	3
Other infections	4	8	11	9	7	7	8
N total	4150	7774	5796	5572	4460	5441	4881

*URTI = Upper Respiratory Tract Infection

**Includes both acute and chronic bronchitis, which are presented separately in papers II and IV

***STD = Sexually Transmitted Disease

Figure 12. *Infection panorama in different age-groups in the MIKSTRA study 1998*
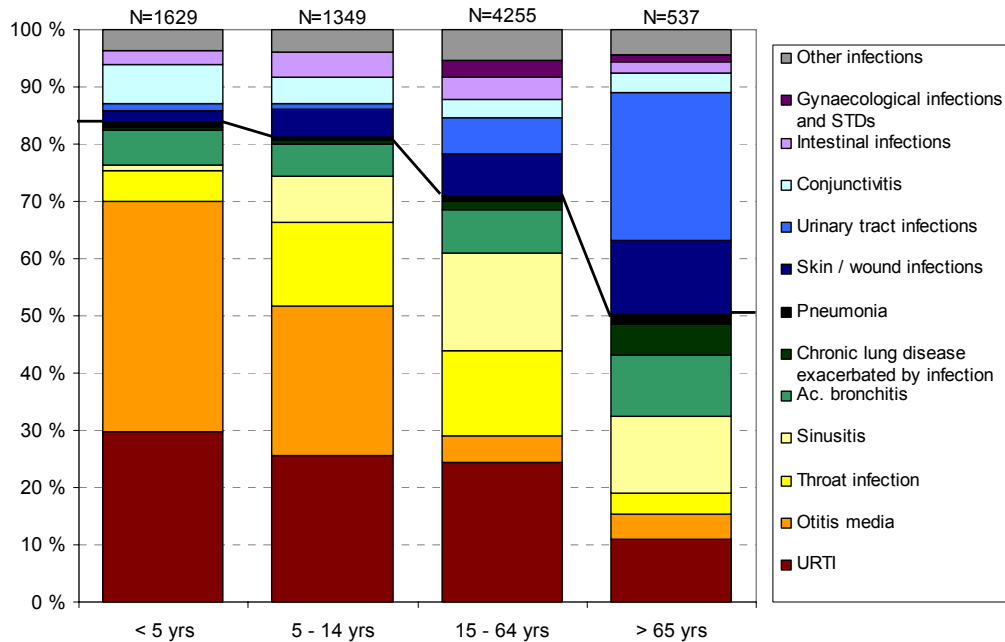
In the Pirkanmaa study the prescribing doctors anticipated that one quarter of the patients expressed a desire to obtain antibiotic treatment, while only 2% opposed the treatment (I). Positive expectations appeared most frequently in diseases with prominent and uncomfortable symptoms, such as gynaecological and urinary tract infections, sinusitis or bronchitis. These expectations were related to patient's age ($p < 0.001$, SAS logistic regression analysis, F-test) and prolonged course of symptoms ($p < 0.01$), especially in bronchitis, pharyngitis and unspecified URTI. Male and female patients did not differ in this respect. On the other hand, pressure from patients to obtain antibiotic treatment did have an effect on doctors: 90% of the patients whom the doctor had anticipated wanting antibiotic actually received it, while 62% of those who were neutral and 32% of those who were against antibiotic treatment received it.

In the Pirkanmaa study, the expectations of the patient were not asked directly from them and so it can be argued as to whether the doctor's anticipation was correct. In the MIKSTRA study, besides asking doctors' perception on patient expectation in the case-report form, also patients were asked about their expectations before their consultation. Patients expressed their wish to get antibiotic in 46% of cases and were against it in 23% (unpublished data), while the corresponding figures for the doctor's anticipation of patient's expectations were 20% wanting and 3% against. When the doctor thought that the patient

expects antibiotic he/she was right in two thirds of cases. On the other hand, doctors recognized correctly only one third of the patients who were expecting antibiotics and less than ten per cent of patients who were against prescribing. This issue will be analysed and presented in more detail in future publications.

Indications for antibiotic use (I, II, IV)

The number of reimbursed prescriptions of antibiotics per 1000 inhabitants in the national prescription register has not changed in the areas of MIKSTRA health centres compared to the national average, although sales in the control health centres area has declined more than average (Figure 13). However, one has to keep in mind that, prescriptions from health centres comprise only part of all the prescriptions delivered from the local pharmacies (50–60%, Klaukka T, personal communication). The number of antibiotic prescriptions per 1000 inhabitants did not decrease notably from 1998 to 2002 (-1.9% in MIKSTRA, -2.5% in controls and +0.6% in the whole country) and the change is also rather small in comparison to 2003 (-4.2, -4.5 and -1.8% respectively). What has happened is that the variation in the volume of sales of antibiotics between the study health centre areas of different sizes has narrowed, from 15% in 1998 to 6% in 2003, and that of individual MIKSTRA health centres from 45% in 1998 to 33% in 2003.

Figure 13. *Number of reimbursed prescriptions of antibiotics (J01) in national prescription register1998–2003 in the whole country, in Pirkanmaa, and in the areas of all MIKSTRA- and control health centres and MIKSTRA health centres grouped according to their size (small, medium, large)*
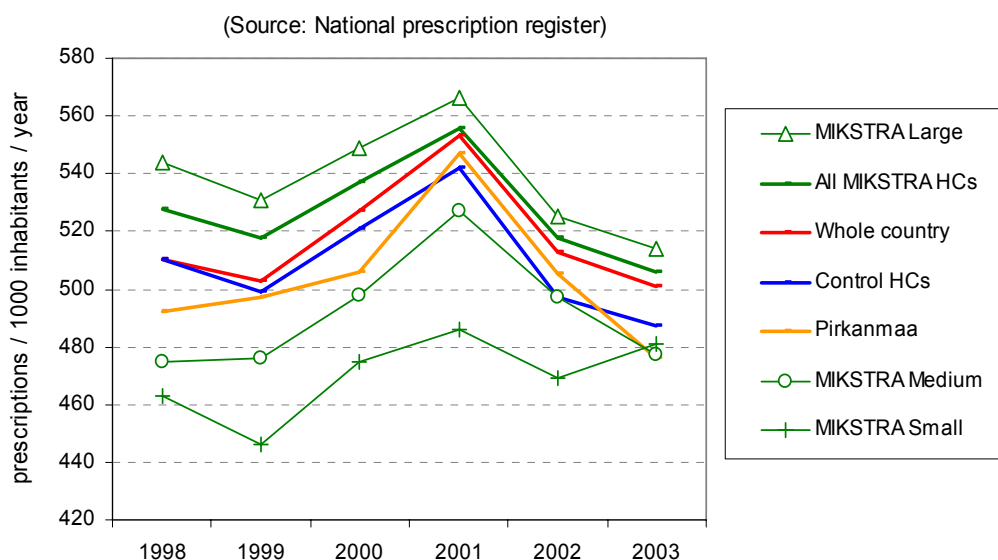
Prescription rate

Of all patients with infection, 64% received antibiotic treatment in the Pirkanmaa study (I). In the first MIKSTRA data four years later average prescribing rate was almost ten per cent lower (Table 11) when only visits to doctors are included (to be comparable with the Pirkanmaa study).

Table 11. Percentage of infection patients who were prescribed antibiotics in Pirkanmaa 1994 and in MIKSTRA 1998–2002 (only visits to doctors included except for last row)

| Diagnosis	Pirkanmaa 1994	MIKSTRA study and control health centres					
		1998	1999	2000	2001	2002	Controls 2002
	%	%	%	%	%	%	%
Unspecified URTI*	10	12	9	15	9	9	10
Otitis media	93	88	82	87	88	91	87
Tonsillitis	86	57	61	58	59	60	61
Pharyngitis	21	17	17	22	20	20	20
Sinusitis	93	83	84	87	89	88	88
Bronchitis	83	70	59	73	69	74	71
Pneumonia	85	63	71	79	89	79	66
All respiratory tract infections	63	57	51	56	56	57	55
Skin infections	83	71	68	72	75	77	72
Urinary tract infections	95	90	90	92	91	88	88
Other infections	35	16	16	13	14	14	16
All infections	64	55	50	54	56	54	54
Variation between health centres	51–76	30–72	27–75	34–73	40–73	38–88	42–76
All infections (incl. nurses)	-	48	45	49	51	46	43

*URTI = Upper Respiratory Tract Infection

Taking into account all consultations for an infection, including those with nurses, less than half of all infection patients received antibiotic prescription in all but one data collection in the MIKSTRA study. Unspecified upper respiratory tract infections and pharyngitis (tonsillitis considered separately) were relatively

74

rarely treated with antibiotics in 1994 and the situation was likewise similar during the MIKSTRA study period. For all other infections, prescribing seemed to be more restrictive in MIKSTRA compared to the Pirkanmaa study. However, nearly all patients with otitis media (82–93%), sinusitis (83–93%) or urinary tract infection (88–95) received antibiotics and the prescription rate was quite high also in bronchitis (59–83) and skin infections (68–83%).

Although children are high consumers of antibiotics according to the prescription register it is not because they were prescribed antibiotics more readily than older patients. On the contrary, the younger the patient was, the more restrictively doctors seemed to prescribe antibiotics (Figure 14, unpublished data). While children under five received antibiotics in less than half of their consultations, elderly people were prescribed antibacterials in 62–68% of cases.

Figure 14. *Proportion of patients who were prescribed antibiotics in MIKSTRA health centres by age and gender; all patients and all years 1998–2002, N=29 256*
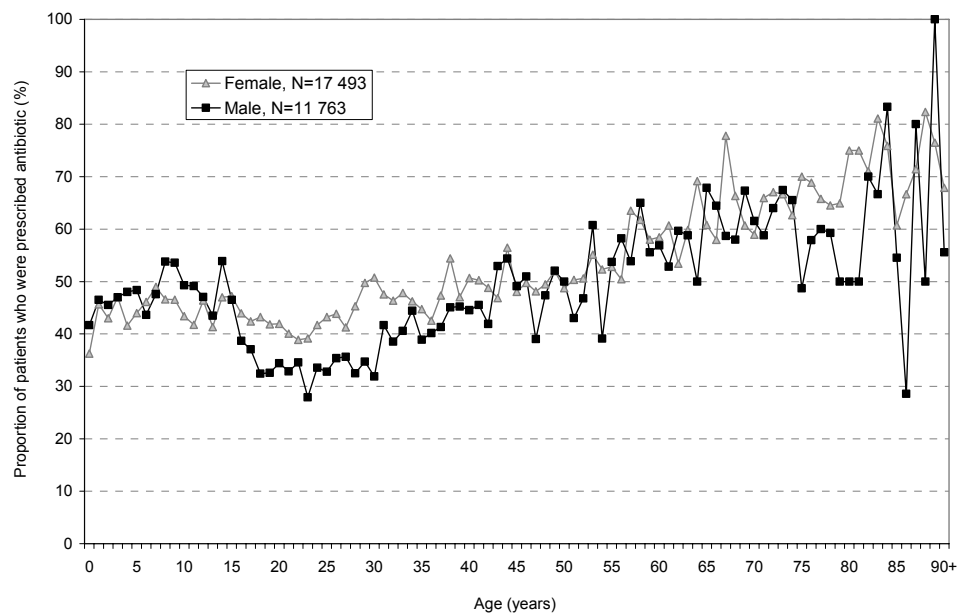
Which indications are antibiotics prescribed for?

Of all antibiotics prescribed in primary health care, almost 80% were, over the years, uniformly for respiratory tract infections (76–79%). Of individual antimicrobial classes, only quinolones were used mainly for infections other than those of respiratory tract both in Pirkanmaa in 1994 as well as in MIKSTRA in 1998 (in 94% and 95% of cases respectively) (I and II). In the Pirkanmaa study

59% of cephalosporins were used for RTIs, while in the first year of the MIKSTRA study their proportion had decreased to 45% (II) and it came down even further to 37% in the following years (unpublished data). Some 20–25% of sulfa-trimethoprim combinations and less than 10% of penicillins, macrolides and tetracyclines were used for other infections than RTIs.

In the Pirkanmaa study, cephalosporins were the most often prescribed antibiotics (19%) followed by amoxicillin (17%), penicillin-V (17%), and doxycycline (16%). In MIKSTRA in 1998, amoxicillin had risen to the top with a proportion of 25% (plus amoxicillin with clavulanic acid 2%, which was used hardly at all in Pirkanmaa), followed by cephalosporins (16%), macrolides (15%) and doxycycline (13%). The distribution of antimicrobials used in adults and children differed to some degree due to the different infections (II). Doxycycline was the most commonly prescribed antimicrobial agent for adults (20% of all antimicrobial prescriptions), followed by cephalosporins (18%), while amoxicillin (45%) and macrolides (18%) were the most popular ones in children. During the follow-up years in MIKSTRA, the proportions of amoxicillin, amoxicillin with clavulanic acid, and macrolides continued to rise while those of cephalosporins, penicillin-V and sulfa-trimethoprim combinations continued to decline (Figure 15).

Figure 15. *Proportion of different antibiotics in Pirkanmaa 1994 and in MIKSTRA over years 1998–2002, all indications*
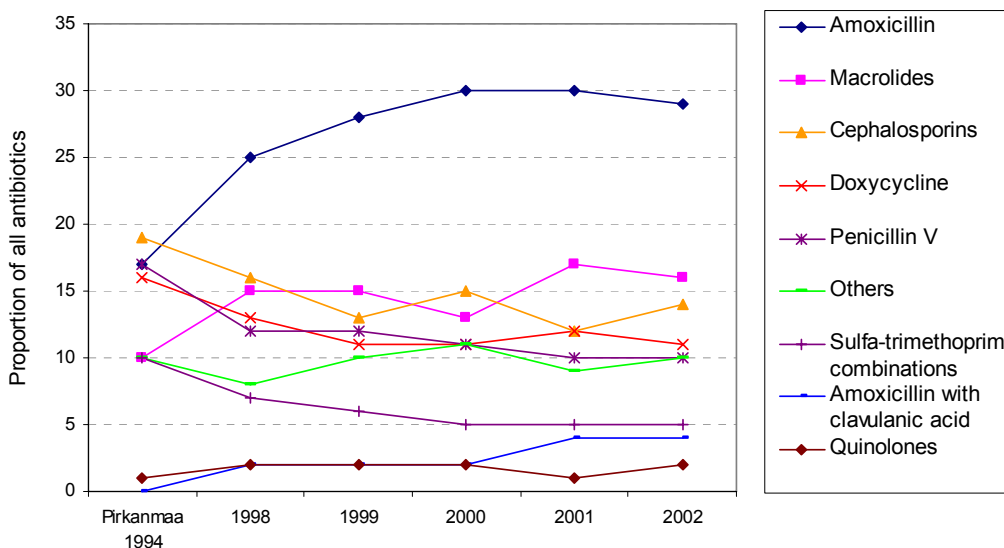

Skin infections comprised 30% of all use of cephalosporins in the Pirkanmaa study, followed by otitis media 23%, tonsillitis 12% and sinusitis 11%. In 1998 MIKSTRA study almost half of all cephalosporins (46%) were used to treat skin infections and generous ten per cent were used for throat infection, otitis media

and sinusitis respectively. During the following years 1999–2002, the proportion of skin-infections have increased up to 54%, that of throat infections has remained even and those for otitis media (9–11%) and sinusitis (6–8%) have even seen a declining trend (unpublished data). In Pirkanmaa, three quarters of the cephalosporins were first-generation preparations (cefalexin or cefadroxil) and the rest were second-generation (cefaclor or cefuroxime axetil). In the MIKSTRA data, the first generation already comprised more than 90% of all cephalosporins (91% in 1998 and 95, 93, 97 and 97% during following years 1999–2002 respectively) (unpublished data)

When comparing data from Pirkanmaa and MIKSTRA 1998, i.e. before the intervention, it seemed that amoxicillin and macrolides had virtually taken the place of cephalosporins and sulfatrimethoprim in the treatment of otitis media and sinusitis. While in Pirkanmaa, cephalosporins comprised 20% and macrolides 2% of antibiotics used to treat otitis media, corresponding figures were 8% and 16% respectively in MIKSTRA. In treatment of sinusitis, the proportion of cephalosporins had decreased from 14% in 1994 to 9% in 1998 and macrolides increased from 7.5% to 15% respectively. The same trend continued during the MIKSTRA Programme (Figure 16).

Figure 16. *Antibiotics selected for treatment of otitis media and sinusitis in Pirkanmaa 1994 and MIKSTRA 1998 and 2002*
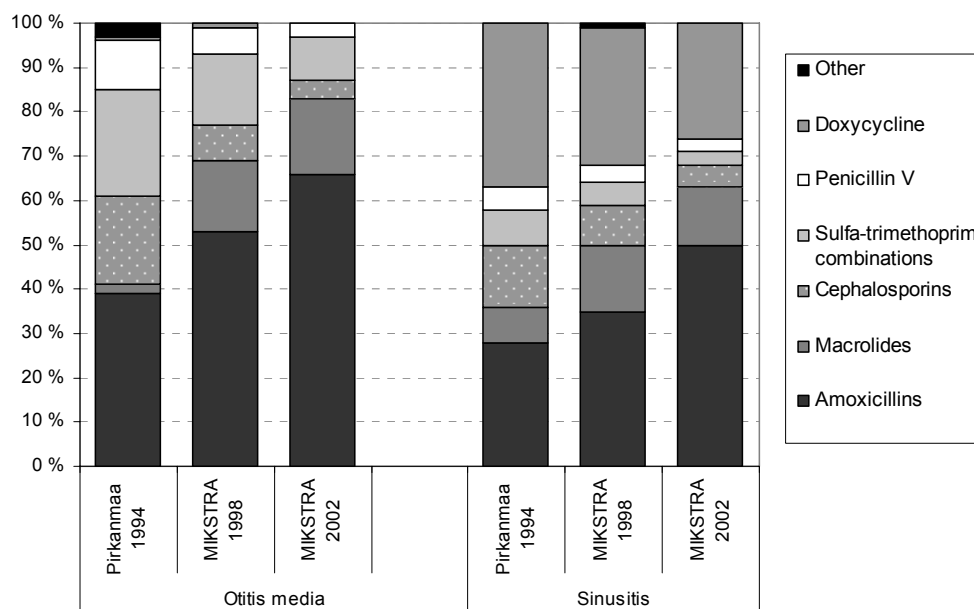
In the Pirkanmaa study macrolides were mainly used for lower respiratory tract infections, bronchitis (44%) and pneumonia (14%). In the 1998 MIKSTRA data 1998 pneumonia comprised only five per cent and other LRTIs 31% of all

indications for use of macrolides, while half of them were used to treat otitis media or sinusitis. The situation has remained similar in MIKSTRA in the years that followed (unpublished data). Eighty-two per cent of all macrolide use was for otitis media (29%), acute bronchitis (24%), sinusitis (21%) and unspecified URTI (9%) (Figure 17; unpublished data).

Figure 17. *Indications of use of macrolides in the MIKSTRA study 1998–2002 (pooled, N=2103)*
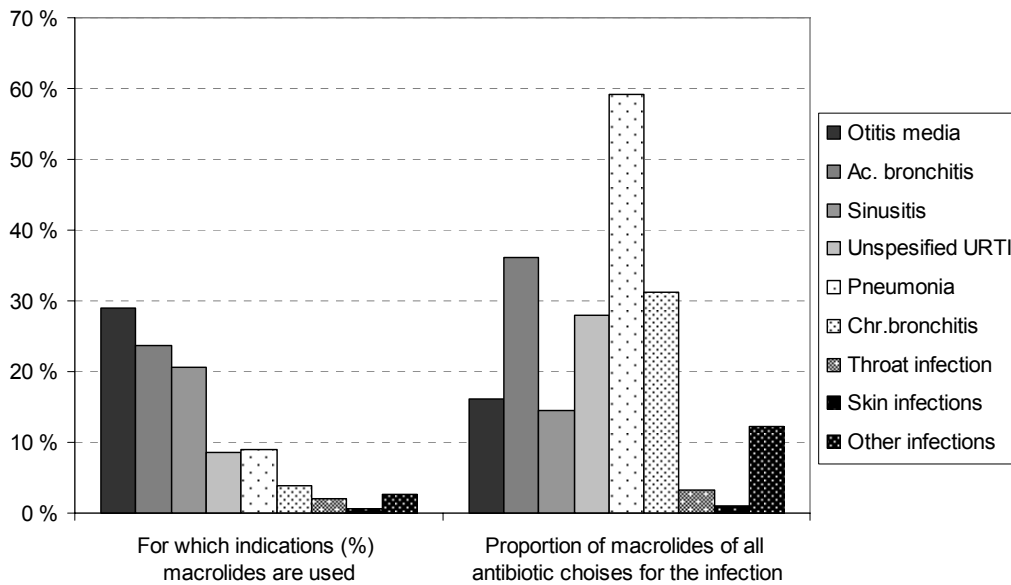
The new generation macrolides, roxithromycin and azithromycin, comprised two thirds of prescriptions in the macrolide group (43% and 26%, respectively) in 1994 (I). Azithromycin had acceded to the leading position within this group in MIKSTRA in 1998 representing 65% of all macrolides, while roxithromycin was the second (26%) followed by clarithromycin (7%) and erythromycin (2%). In 2002 data the new generation macrolides had practically replaced erythromycin. When upper respiratory tract infections were treated with macrolides, azithromycin was selected in most cases, while roxithromycin was the most commonly used macrolide in lower respiratory tract infections.

Half of the sulfa-trimethoprim combinations in 1994 and more than sixty per cent in 1998 were used to treat otitis media, which in practice means treating children (I and II). Urinary tract infections and sinusitis both comprised generous ten per cent of the use of this antimicrobial substance.

Doxycycline was practically the only tetracycline preparation used both in Pirkanmaa and in the MIKSTRA study. Half of all tetracycline use was for sinusitis and a third for acute (29%) or chronic (4%) bronchitis. Skin-infections,

78

including treatment of acne with prolonged courses of tetracyclines, comprised less than 3% of all tetracycline prescriptions.

Use of diagnostic aids and comparison to current recommendations (III)

The use of diagnostic tools was studied in first consultations for an episode of respiratory tract infection in the MIKSTRA health centres in 1998, i.e. prior to publishing the guidelines, to establish baseline data for the guidelines implementation. Of the 7774 infectious disease cases, 6121 (79%) were first consultations and 4386 of them were due to a respiratory tract infection.

Some diagnostic tests were used in 40% of all cases of respiratory tract infections but the use of tests varied remarkably between diseases. Tympanometer was available in one third of the MIKSTRA study health centres but it was used in acute otitis media only in eight cases out of 915. Almost all health centres had an ultrasound device available and it was widely used. In sinusitis, ultrasonography, sinus radiography or both were carried out in most cases (81%). Throat culture, antigen detection or both were obtained in 57% of throat infections. In acute bronchitis a radiography as well as white blood cell count was taken in five per cent of patients, and C-reactive protein was assayed in eight per cent. The corresponding figures in pneumonia were 49%, 27% and 39% respectively.

Antimicrobials were prescribed to 52% of those who had been tested, and to 51% of those not tested, (p=0.589). When the association between the use of diagnostic tests and prescriptions was analysed in more detail it seemed that management patterns varied by diagnosis. In pneumonia, 87% of those tested with chest radiography, white blood cell count or C-reactive protein, received antimicrobials, compared to only 50% of those not tested (p=0.016). In bronchitis the corresponding figures were 64% and 73% for the tested and not tested patients, respectively (p=0.215). In throat infections antimicrobials were prescribed to 41% of patients tested with either antigen detection or culture versus to 50% of those not tested (p=0.015). In sinusitis 89–90% of patients received antimicrobials regardless of testing (p=0.878). The results of the diagnostic tests used were not recorded in the case report forms, which limits the conclusion about the guiding effect of the use of diagnostic tests towards correct antimicrobial prescription. Compared to the new treatment guidelines diagnostic tests were under-used in most cases except in sinusitis (Table 15)

According to the follow-up questionnaire on basic information in 2002, only one health centre had bought a tympanometer since 1998 while the number of ultrasound devices has remained unchanged. The use of these diagnostic aids had not increased either. In bronchitis and throat infection the use of diagnostic tests had increased slightly (Table 12).

Table 12. Comparison of the recommendations given in Finnish evidence-based clinical guidelines on diagnostic methods in four respiratory tract infections and the use of diagnostic aids by GPs in MIKSTRA health centres

Disease Methods of diagnosis according to guidelines	Use of a relevant test by GPs before guidelines* (after intervention)**	Conclusions on comparison of practice and recommendation
Otitis media Symptoms of acute URTI and detection of middle ear effusion with pneumatic othoscope complemented with tympanometry	Tympanometry 1% (<1%)	Notably underused
Throat infection Detection of Streptococcus A by culture or antigen detection	Culture 37% (42%), antigen detection 24% (30%)	Slightly underused
Maxillary sinusitis Symptoms of acute sinusitis and detection of maxillary effusion by ultrasonography or x-ray	X-ray 5%, Ultrasonography 74%	In line with the recommendation
Bronchitis Clinical symptoms and signs; if antibiotic treatment is considered elevated C-reactive protein supports the decision to prescribe	C-reactive protein 8% (11%)	Notably underused

* MIKSTRA 1998
**MIKSTRA 2000–2002 (short reports published in Finnish at Lääkeinfo-column in Finnish Medical Journal)

Effect of implementing guidelines (IV)

The implementation of guidelines in MIKSTRA faced several unexpected problems. First, the unpredicted crisis in primary health care with the exodus of doctors from health centres caused a tremendous change of doctors during the five years of the study (Table 8, page 65). Secondly, the key person in the educational intervention became seriously ill and was replaced only after an eight-month break. Because of this, the health centres received the educational

tools to aid the local activities as well as methodological support not until in the summer of 2000 onwards, almost a one-year delay from the beginning of the intervention and from the original plan. As a consequence, the health centres had problems in following the protocol as expected. Eventually, slightly more than a third of health centres fully realized the program, as recommended by the MIKSTRA research group, five completely and eight with only minor deviation. Fourteen health centres modified the training method and/or timing substantially, and three health centres were not able to start the program at all. The randomisation to groups A and B was broken and the original plan of health centres being controls to each other in the 2000 data collection was lost. Illustratively also, although it was recommended to document the collectively agreed local practices during the implementation process, this was realized in less than half of the study health centres.

In the first data collection after the educational implementation in 2001, 218 physicians in the study health centres, 58% of all physicians participating in the data collection that year, reported that they had participated in the MIKSTRA-training. About half of the doctors (183 doctors, 49%) had also participated in the 1998 baseline data collection. In the 2002 follow-up, the corresponding figures were 249 (61%) for those who had participated in training and 184 (45%) for those who had also participated in data-collection in 1998. The analyses were made, however, according to the original protocol, on an intention-to-treat basis.

The main outcome measures in assessing the success of guideline implementation were the concordance of prescribing practice with the guidelines in respect of selecting first-line antibiotic choice and recommended duration of treatment (Table 13). Secondary outcome measures were the proportion of patients who were prescribed antibiotics by infection and use of relevant diagnostic tests, which was discussed above.

Table 13. Recommendations for first-line antibiotic and duration of treatment in the Current Care -guidelines for otitis media, tonsillitis, sinusitis, acute bronchitis, bacterial skin infections and urinary tract infections, implemented in MIKSTRA programme

Diagnosis	Recommended first-line antibiotic	Recommended duration of treatment
Acute otitis media	amoxicillin or penicillin-V	5 days
Streptococcal tonsillitis	penicillin-V	10 days
Acute sinusitis	amoxicillin	7 days
Acute bronchitis	primarily none, if specially justified then penicillin-V	5–7 days
Bacterial skin infections	I[st] generation cephalosporins	not specified
Urinary tract infection (female uncomplicated)	nitrofurantoin, pivmecillinam or trimethoprim	3–5 days

The proportions of use of the recommended first-line antibiotics at the first consultation for the infection episode increased in all infections. The increase was significant in sinusitis (P <0.001), acute bronchitis (P= 0.015) and urinary tract infections (P= 0.009). At the follow-up in 2002, however, there were no significant differences between the study and control group health centres.

In all other infections except streptococcal throat infection, new guidelines recommended shorter courses of antibiotics than had been traditionally used in Finland. After the intervention in the study group health centres, the proportion of antibiotic treatments with recommended (shorter) duration had significantly increased in otitis media (P <0.001), sinusitis (P <0.001) and in urinary tract infections (P= 0.042). Azithromycin was excluded from this analysis because it is always used in short courses.

The overall concordance with the recommendations of antibiotic treatment in respiratory tract infections was analysed separately (Table 14). Prescribing for respiratory tract infections, in line with the recommendations, increased in the study health centres from 20.6% in 1998 to 27.0% (P <0.001) in 2001 but there was no significant difference between the study and the control health centres in 2002.

Almost half of all antibiotic prescribing for respiratory tract infections was not in line with the recommendations. One fifth of all antibiotics were prescribed for infections for which they are not recommended, mainly acute bronchitis (63–67%). This did not change during the intervention period. About one quarter were prescribed for accepted indications (otitis media, tonsillitis or sinusitis) but other than first-line drug was used without a given justification of allergy or other previous side-effect related to the drug of choice. From the 1999 data collection onwards, other justifications were elicited (preceding antibiotic treatment, chronic or relapsing or prolonged infection, immunocompromised patient, test-results or other epidemiologic information). These justifications decreased the proportion of unjustified prescribing for pharyngitis, UTRI and bronchitis with 2–3 per cent units (to 18%) and unjustified use of other than first-line drug with 8–9 per cent units (to 17-19%) and decreased the total proportion of prescribing not in line with the recommendations to just below 40% (unpublished data).

In general, when other than a first-line drug was selected for treatment in otitis media, sinusitis or tonsillitis, it was only seldom (on average in 23 per cent of cases) justified by an allergy or other side effect. Justification for selection of other than first-line drug was given somewhat more often in tonsillitis (40% of cases) than in the other two infections.

Antibiotic treatment for otitis media was in line with the recommendations in nine per cent of cases before the intervention (1998) but in 22% after it (2001) and in 19% at the follow-up (Table 15) and 15% in the control health centres (unpublished data). Corresponding figures for sinusitis were 32% before, 45% after and 39% at the follow-up and for the controls. Treatment of streptococcal tonsillitis better adhered to guidelines already prior to the intervention: 71% before, 72% after and at the follow-up, 79% with the controls. Treatment of otitis

82

media differed from the recommendation in most cases (45–55% of cases) only in respect of the duration of treatment with the recommended antibiotic. In one third of cases, deviation was due to unjustified selection of other than first-line drug. In the case of sinusitis the situation was the opposite: in 41–51% of cases other than first-line antibiotic was chosen without giving justification for the decision (Table 15).

Table 14. Overall correctness of prescribing for respiratory tract infections in MIKSTRA study and control health centres before and after implementation of guidelines

	MIKSTRA health centres						Control health centres	
	1998 before		2001 after		2002 follow-up		2002	
	N	%	N	%	N	%	N	%
Prescribing in line with the recommended ('correct') in all aspects	579	20,6	459	27,0	455	24,9	384	25,4
Correct indication, antibiotic and duration								
otitis media (amo/pen-V, 5 days)	10	<1	70	4	70	4	34	2
sinusitis (amo, 7 days)	128	5	178	10	139	8	102	7
streptococcal tonsillitis (pen-V, 10 days)	210	7	77	5	106	6	111	7
Correct indication, antibiotic other than first-line, but justified otitis media	84	3	60	4	52	3	43	3
sinusitis	113	4	63	4	70	4	80	5
streptococcal tonsillitis	34	1	11	1	18	1	14	1
Correct indication and antibiotic, duration other than recommended	725	25,9	352	20,7	417	22,8	329	21,7
otitis media	560	20	263	15	316	17	251	17
sinusitis	118	4	74	4	78	4	67	4
streptococcal tonsillitis	47	2	15	1	23	1	11	1
Antibiotics for pneumonia and infection exacerbated chronic lung disease	110	3,9	113	6,6	110	6,0	60	4,0
Correct indication, antibiotic other than first-line drug without justification	792	28,2	435	25,6	461	25,2	404	26,7
otitis media	362	13	194	11	197	11	158	10
sinusitis	379	14	222	13	239	13	224	15
streptococcal tonsillitis	51	2	19	1	25	1	22	1
Antibiotic not recommended	598	21,3	343	20,2	378	21,1	336	22,2
viral pharyngitis	50	2	30	2	32	2	34	2
unspecified URTI	163	6	82	5	95	5	92	6
acute bronchitis	385	14	231	14	260	14	210	14
Total number of prescriptions	2804	100	1702	100	1830	100	1513	100

Table 15. Correctness of prescribing for individual respiratory tract infections in MIKSTRA study and control health centres before and after guidelines implementation

| | MIKSTRA health centres | | | | | | | | | Control health centres | | |
| | 1998 before | | | 2001 after | | | 2002 follow-up | | | 2002 | | |
	N	% total	% subtotal	N	% total	% subtotal	N	% total	% subtotal	N	% total	% subtotal
Otitis media	1016	36	100	587	34	100	635	35	100	486	32	100
recommended antibiotic and duration	10	<1	1	70	4	11	70	4	11	34	2	7
other than first-line antibiotic, justified	84	3	8	60	4	10	52	3	8	43	3	9
recommended antibiotic, other duration	560	20	55	263	15	45	316	17	50	251	17	52
other than first-line antibiotic, not justified	362	13	36	194	11	33	197	11	31	158	10	33
Sinusitis	738	12	100	537	17	100	526	14	100	473	14	100
recommended antibiotic and duration	128	5	17	178	10	33	139	8	26	102	7	22
other than first-line antibiotic, justified	113	1	15	63	1	12	70	1	13	80	1	17
recommended antibiotic, other duration	118	4	16	74	4	14	78	4	15	67	4	14
other than first-line antibiotic, not justified	379	2	51	222	1	41	239	1	45	224	1	47
Streptococcal tonsillitis	342	27	100	122	22	100	172	24	100	158	28	100
recommended antibiotic and duration	210	7	61	77	5	63	106	6	62	111	7	70
other than first-line antibiotic, justified	34	4	10	11	4	9	18	4	10	14	5	9
recommended antibiotic, other duration	47	2	14	15	1	12	23	1	13	11	1	7
other than first-line antibiotic, not justified	51	14	15	19	13	16	25	13	15	22	15	14
Antibiotics for pneumonia and infection exacerbated chronic lung disease	110	4		113	7		110	6		60	4	
Antibiotic not recommended	598	21	100	343	20	100	387	21	100	336	22	100
Viral pharyngitis	50	2	8	30	2	9	32	2	8	34	2	10
Unspecified URTI	163	6	27	82	5	24	95	5	25	92	6	27
Acute bronchitis	385	14	64	231	14	67	260	14	67	210	14	63
Total	2804	100		1702	100		1830	100		1513	100	

DISCUSSION

This thesis describes the development, testing and implementation of a survey method for monitoring antibiotic use in the community. To my knowledge MIKSTRA has been the first attempt word-wide to make a nationally representative survey on the management of infection patients and antibiotic use and to systematically evaluate the long-term influence of nationally implemented guidelines. The quality of antibiotic prescribing improved in the MIKSTRA study health centres during the implementation period, although there was no statistically significant difference in performance compared to the control health centres at follow-up. This study gives an insight into the management of infections in primary care as a whole. Furthermore, the study's detailed information provides the necessary basis needed for further development, both in terms of updating and implementing guidelines and designing future antibiotic policy.

Study limitations

As the diagnostic criteria were not standardised in this study and the results of diagnostic tests were not recorded, it is not possible to assess if the diagnoses were set correctly and similarly by all doctors and during all years. It is not possible either to rule out that doctors may have shifted diagnoses towards those for which antibiotic prescribing is recommended, although the similarity of the distribution of diagnoses over the years does not suggest this to have been the case. There is also no reliable source of reference that could be used to calculate the true proportion of all infection patients entered in the Pirkanmaa and MIKSTRA studies.

   MIKSTRA study health centres represented a substantial proportion of the population of the country and they were selected to represent different sizes, types and geographical locations. It is possible, however, that as they were selected from those 82 health centres which expressed their interest to participate, they may have been different from those who were not interested.

   The control group of health centres in the MIKSTRA study may have been biased in the sense that after the drop-out the remaining health centres represented lower antibiotic consumption areas. When the randomisation of the MIKSTRA study health centres was broken thereby undermining the internal control as-well, it would have been important to have also collected base-line

data from the control health centres - despite the fact that data-collection would have been an intervention as such.

Representativeness of the sample

The good coverage of the study and compliance of the physicians in the health centres was a good example of the functionality of the organising of Finnish health care and the commitment of its staff. None of the health centres dropped out and the participation rate was satisfactory, at over 80 per cent throughout the five years of MIKSTRA. We do not have detailed data on the non-responding doctors. There might have been a true non-response, though doctors may also have been temporarily off work for holiday, training or sick leave, and as we know, there was a shortage of doctors in some health centres.

The average number of case-report forms completed by each doctor was 11–27% lower in 1999–2002 compared to that in 1998. Part of the decline is explained by the absence of on-call services in Turku from 1999 onwards and in Oulu from 2000 onwards as these two health stations comprised 14% of all consultations for infections in 1998. Higher proportion of infection patients is typical of on-call services. Until recent years, these services have been provided, during evening and night time, by the same doctors that are working elsewhere in the health centre during the day time. Leaving on-call services outside the data collection in two big cities appears to have led to fewer overall patients per doctor. The rest of the decline in patients per doctor in the data may represent research tiredness, or true differences in the point prevalence of consultations for infections, though it is not possible to verify this with this data collection method.

The rapid emergence of a shortage of doctors and especially their exodus from the health centres during the programme was an unexpected phenomenon. In the whole country, in 1993–1995 all GP posts in health centres were still filled and thus from 1996–1998 this was not even studied by the Finnish Medical Association. In 1999 deficit of doctors had reached a national average of five per cent and in the consecutive years from 2000–2002 it was seven, nine and eleven per cent respectively (Vehkasaari, 2002), while the MIKSTRA study and control health centres reported an average of eight per cent deficit of doctors in 2002.

Furthermore, the health centres reported that 40% of their doctors had changed between 1998 and 2002 and about one fifth of their GP posts were hosted by a temporary substitute in 2002. This turnover among personnel explains why half of all 953 doctors, who participated in the data collection in the MIKSTRA health centres during the five years of the study, participated only once. The heavy turnover of doctors in health centres probably did not harm the quality of the annual data as such but had definitely an effect on the influence of the intervention when analysed on an intention-to-treat basis.

In comparison to the national register of prescriptions, our data-collection covered on average 73% of all prescriptions prescribed by the 454 doctors identified in both sets of data during the 1998 study week. The coverage can be considered satisfactory given the gaps that both data sources have. Some less expensive antibiotics like penicillin-V were underrepresented in the prescription register, compared to the MIKSTRA data, but on the other hand it contained drugs that had been delivered by prescription to nursing homes, which were excluded from our data and thus were underrepresented there. These were mainly substances used for UTI, especially methenamine. Many doctors are also working in the private sector or doing extra on-call service in other health centres in addition to their permanent post. All their prescriptions prescribed at any location during the study week are included in the national prescription data but only those prescribed in a MIKSTRA health centre are in our data.

The final conclusion is that the data-collection method was acceptable and feasible and that it gave a representative picture of the true prescribing situation in the health centres of the study area.

Infections

Most consultations for infections were out-of-hour visits. In the Pirkanmaa study we received the total number of out-of-hour visits in the health centres during the study week and could calculate that 37% of all these visits were due to infections. This is in line with the results obtained elsewhere (Arinen et al., 1998, Hemminki et al., 1974).

Only two per cent of infection patients were referred to secondary care, which is less than the average referral rate for all indications (5%) in Finland (Vehviläinen et al., 1996, Vehviläinen et al., 2005). Despite this, infections comprise a remarkable part of indications of referral especially in children. If only about half of the patients with infections seek medical attention (Adams et al., 1999, Aromaa & Koskinen, 2002) and two per cent of these attended are referred, it is obvious that the infection patients seen in secondary care are only the tip of the iceberg and highly selected. This should be kept in mind when drawing conclusions across studies made on the common infections in both secondary and primary care.

The overwhelming majority of community acquired infections are those of the respiratory tract. The distribution of diagnoses was very similar over the years in MIKSTRA. The only major difference in the distributions in the Pirkanmaa and MIKSTRA studies seemed to be the remarkably higher prevalence of bronchitis in the Pirkanmaa study (14%) compared to the MIKSTRA data (7–9%). Although the Pirkanmaa study is not nationally as representative, and there may be individual and local differences in establishing this diagnosis, the difference raises interesting questions. The epidemiologic situation could be possible, but not very probable explanation to this.

Information on epidemics of major bacterial pathogens in Pirkanmaa in November 1994 is not available. Instead, according to the infectious diseases register, there were epidemics of pertussis at the end of 1999 and 2000 and of M*ycoplasma pneumoniea* at the end of 2001 and 2002 in the national data, i.e. during most MIKSTRA data collections. Perhaps a more probable explanation on the different prevalence is that still in 1994 it was more common than during MIKSTRA study to label a patient with URTI with intense or prolonged cough as having bronchitis to justify prescribing of an antibiotic.

The concept of acute bronchitis is problematic. It resembles closely upper respiratory infections, and the diagnosis may in many cases be a mere excuse for antimicrobial prescription (Gonzales et al., 1998, Hueston et al., 2000b). Such a tendency has been found also when comparing low prescribing and high prescribing doctors in Canada (Hutchinson et al., 2001), in Belgium (De Sutter et al., 2001) as well as in MIKSTRA (Leistevuo et al., 2005): high prescribing doctors tend to set more diagnoses of bacterial infections and bronchitis than low prescribing doctors. After publishing the results of the Pirkanmaa study, antimicrobial resistance, over prescribing of antibiotics in general and to acute bronchitis in particular was visibly discussed in the media as well as in the Finnish Medical Journal, which may have had an influence on general attitudes and gradually on prescribing practices. A similar decline in the proportion of acute bronchitis among infection diagnoses has been seen in intervention studies elsewhere (Gonzales et al., 1999, Stewart et al., 2000, Welschen et al., 2004b) - but not always (Hueston & Slott, 2000).

The proportion of unspecified URTIs and intestinal infections were somewhat higher in MIKSTRA than in the Pirkanmaa study. This may be due to the fact that nurses were included in MIKSTRA but not in Pirkanmaa. Nurses managed on average 14% of all infection patients in MIKSTRA health centres in 1998–1999 (Rautakorpi et al., 2002). About half of all patients with intestinal infections and a quarter of patients with unspecified URTI met only a nurse when they visited the health centre. With the increasing shortage of doctors in health centres it seems reasonable that these groups of infection patients, who in most case only need advice and support or a medical statement for sick leave, are managed by nurses.

Use of diagnostic aids

Acute respiratory tract infections are more or less one entity. They are closely related and share similar symptoms, pathogenesis and aetiology. Instead of identifying the specific etiologic agent, the clinician's main problem is usually whether the probable agent is treatable with antimicrobials or not. Clinical signs are in most cases unhelpful, as they differ little in bacterial and viral infections. The diagnosis, however, rules the management of the patient from that point on and is the key to correct treatment. The frequency of using adequate diagnostic

tools also reflects the quality of the professional diagnostic and decision making process.

The use of diagnostic aids was most frequent (81%) in sinusitis and least frequent in acute otitis media (8%) (referring to other than pneumatic otoscopy, which was regarded as a self-evident basic tool). Compared to the recommendations given in the guidelines, tests were clearly under-utilised as a support for treatment decisions in all other infections except in sinusitis (Table 12, page 79). As the actual decision in common respiratory tract infections is whether the patient benefits from an antibiotic or not, in order to be useful, the diagnostic test must influence prescribing. In our study, testing was associated with less frequent use of antimicrobials in throat infections, but in pneumonia, the association was the opposite. Thus, physicians may either test to avoid antimicrobial treatment (as in tonsillitis in our study) or to reliably recognise a serious disease (as in pneumonia).

The results of the diagnostic tests used were not recorded in the case report forms, which limits the conclusions that can be drawn about the guiding effect of the use of diagnostic tests. In previous studies the guiding effect of tests has been found to be poor or non-optimal (Andre et al., 2004, Mäkelä, 1989, Melbye et al., 1995). The diagnostic process is neither entirely rational nor based on biomedical factors alone. Other determinants like workload, social pressure and fear of complications also guide the decision-making process (Howie, 1983).

Although the use of tympanometry in otitis media did not increase and the use of throat swab in throat infections increased only moderately, there was a slight trend in the MIKSTRA health centres towards more common cold and less otitis media and throat infection. Such a trend could be expected as a consequence of improved diagnostics. A similar phenomenon was seen in Iceland at the beginning of 1990s when the increased resistance of pneumococci led to a recommendation to restrict prescribing of certain antibiotics for otitis media. A concurrent decline was seen in the number of diagnosed cases of otitis media in primary care (Kristinsson, 1999) possibly because of more prompt diagnostics.

The diagnoses of otitis media and maxillary sinusitis are established by detecting the effusion in middle ear or in maxillary sinus. The Finnish guidelines suggest that these diseases should be treated with antimicrobials if effusion is present. The correct use of antibiotics in sinusitis requires that the clinician can interpret the ultrasonography and radiography findings reliably (Blomgren et al., 2002, Laine et al., 1998, Mäkelä & Leinonen, 1996, Varonen et al., 2003). In otitis media, use of tympanometry can decrease the number of otitis media diagnoses by as much as one third by providing more accurate diagnostics (Blomgren et al., 2004, Palmu et al., 1999) and can help a clinician to target antimicrobial treatment to those who benefit most from it (Palmu et al., 2001). Tympanometry was used far too seldom in our study to adequately test these hypotheses.

According to Joki-Erkkilä, the incidence of recurrent acute otitis media over a 12-month period seems to have increased in Finland between 1978/9 and

1994/5, while the clinical picture has become milder (Joki-Erkkilä et al., 2000). It can be asked how much of this increase is due to a loosening of diagnostic criteria, where doctors were no longer pushed to use tympanocentesis as a golden standard of diagnostics and the use of tympanometry has not yet been adopted in primary care – and how much is due to the increased number of antibiotic courses predisposing to new infections.

This study demonstrates that everyday routines are in some ways working far from the recommendations in respect of the diagnostics of common respiratory tract infections. In order to get a more precise picture on the concordance of diagnostic practises with the guidelines the association between positive and negative test results and the use of antimicrobials needs to be studied in the future.

Antibiotic prescription

Although Pirkanmaa and MIKSTRA cannot be compared directly it seems obvious that the ten per cent lower proportion of patients who get antimicrobial prescription for an infection in MIKSTRA compared to Pirkanmaa reflects a true change towards more restrictive prescribing. Also, according to the Finnish Statistics on Medicines, the annual antibiotic sales declined 13 per cent from 1994 to 1998 i.e. before the MIKSTRA programme started and there has been an additional decrease of 5.9% since then (Figure 3, page 29).

It is difficult to assess whether MIKSTRA has contributed to this decline or not. In the same period of time there have been even bigger declines reported in other countries in antibiotic prescriptions for acute respiratory tract infections in children (Ashworth et al., 2004, Finkelstein et al., 2003, Kozyrskyj et al., 2004, McCaig et al., 2002, Unsworth & Walley, 2001). These studies also found a remarkable decrease in the number of consultations for mild respiratory tract infections. Something similar may also be going on in Finland, thus explaining why the declining trend in national statistics started already before MIKSTRA. It may also partly explain the decrease in the number of patients in the MIKSTRA study. The authors of the articles from UK, USA and Canada speculate as to whether the decline in the frequency of consultations is due to patients' increased awareness of the nature of illness of mild respiratory tract infection and a subsequent higher threshold before consulting the doctor in connection with it. The Pirkanmaa study brought the issue of unnecessary prescribing and antibiotic resistance into public debate in Finland and MIKSTRA has helped to keep it there since then, which may have had an influence on patients' attitudes.

Prescribing of antimicrobials seemed to be, in general, more restrictive in small, rural MIKSTRA health centres than in urban area, unlike in an Australian study from 1990s where the opposite appeared to true (McManus et al., 1997). The same phenomenon is evident also in the Finnish archipelago - the Åland Islands - where medicines consumption is characterised by low pharmaceutical

consumption and costs in most drug groups (including antibiotics), conservative pharmaceutical choices and characteristic patterns (Lahnajärvi et al., 1997). There might be several possible explanations for this. The incidence of infections may be lower in thinly populated areas. More people are working at home in rural, agricultural areas. They don't need to go to see a doctor for minor infections to get sick leave or it is laborious do so. Families need to take their small children less often to day-care-centres, where children would get more infections, which they would again transmit to their family members (Forssell et al., 2001, Möttönen & Uhari, 1992, Nurmi et al., 1991, Pönkä et al., 1991). On the other hand, distances in Finland, unlike perhaps in Australian rural areas, are perhaps not as long as it would push the patient to demand and the doctor to prescribe antibiotics 'just-in-case'. Furthermore, when doctors and patients are familiar with each other it is easier for the doctor to assess the need for antibiotic of his/her patients and for the patient to rely on the doctors' decision (personal observation). This again helps to avoid 'just-in-case' -treatments and makes it easier to favour even the watchful waiting strategy. And finally, in a rural group practice with stable personnel, doctors' performance may show more coherence and also, due to the distances, will experience less exposure to face-to-face pharmaceutical marketing (Lahnajärvi et al., 1997).

In our study amoxicillin was by far the most commonly used antibacterial followed by macrolides and cephalosporins, while the use of amoxicillin and cephalosporins was rather even in the national data. The differences in the ranking-order do not contradict each other. National sale statistics cover the whole year while our data-collection was a point prevalence survey situated in the high season of respiratory tract infections. Sales of cephalosporins, which are mainly used for skin infections, have hardly any seasonal variation (Figure 18) and they are often used for longer periods of time than antibiotics used for respiratory tract infections. Thus cephalosporins accumulate more in national statistics, while antibiotics such as amoxicillin, which are used mainly for respiratory tract infections, are more represented in our data.

Increasing use of amoxicillin, which was found in our data, was a desired trend and in line with the recommendations, as it is the recommended drug of choice in most respiratory tract infections. Increasing use of amoxicillin with clavulanic acid, on the other hand, does not have a sound basis in the development of the resistance situation and this clearly necessitates some kind of intervention. Unnecessarily prescribing more expensive antibiotics with more side-effects does not benefit the patient and does not constitute good quality of care.

The continuously decreasing proportion of penicillin-V is a somewhat undesirable and unnecessary development. As the most common causative agents in community acquired respiratory tract infections are on the other hand viruses and on the other the potentially dangerous bacteria, *Streptococcus pneumoniae* and *pyogenes*, antibacterial treatment should, in most cases, cover the latter two. Penicillin has maintained its effect in these pathogens in Finland and could obviously be used more often.

Figure 18. *Number of reimbursed prescriptions of antimicrobials by month from January 1998 to March 2003 (Source: National prescription register)*
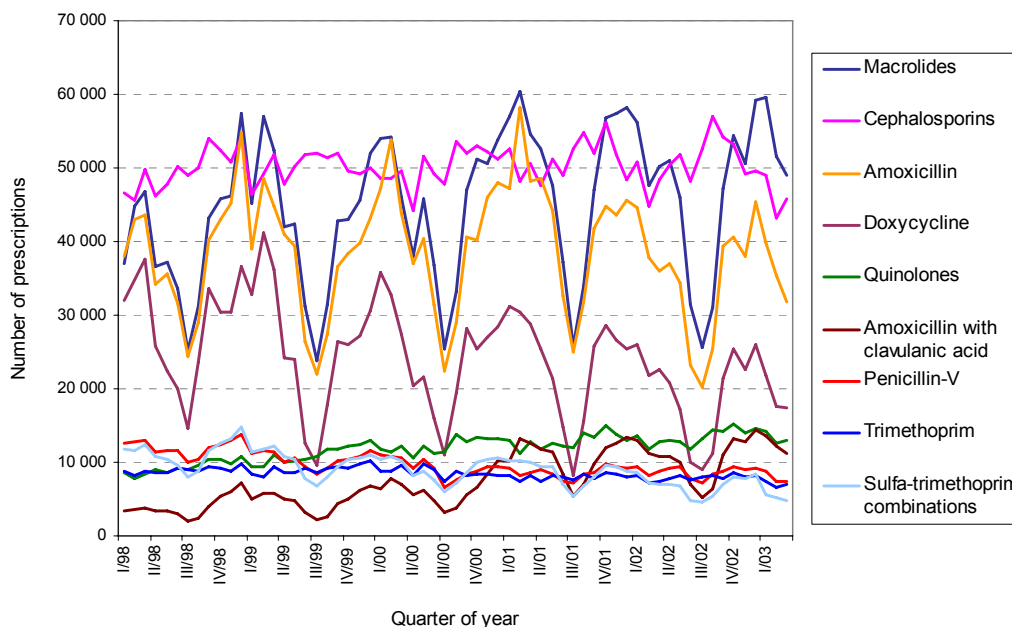
The more ill the patient is with his/her respiratory tract infection, the more probable it is that the causative agent is *Streptococcus pneumoniae*. At this level of macrolide resistance it is probably safer in such cases to treat the patient with penicillin or amoxicillin, (or cephalosporin or doxycycline) than with macrolides. The usefulness of beta-lactams in such cases is also supported by recent meta-analyses of hospitalized patients with community acquired pneumonia, which conclude that empirical coverage of atypical pathogens in primary antibiotic choices does not give benefit in terms of survival or clinical efficacy over beta-lactam antibiotics (Mills et al., 2005, Shefet et al., 2005).

First-generation cephalosporins are recommended in Finland as the drug of choice for skin infections, and in the case of penicillin allergy, for tonsillitis. These diagnoses explained 42% of the consumption in 1994, 59% in 1998 and 65% in 2002. First-generation cephalosporins seldom result in any microbiological benefit compared with firstly recommended drugs in sinusitis, bronchitis or pharyngitis. The proportion of second-generation cephalosporins is low, which is correct as they are recommended only as the second or third option, even though they can be microbiologically justified in some cases of otitis media and sinusitis. Furthermore, it is noteworthy that although cefuroxime axetil represented only 7% (38/516) of all cephalosporins used in the Pirkanmaa study, it accounted for 85% (17/20) of all reported severe cases of cephalosporin-induced colitis in Finland during 1990–1995 (Lumio, 1996). Using such medicine to treat common, mild or self-limiting respiratory infections cannot be justified when safer alternatives are available.

The proportion of macrolides among all antibiotics was only slightly rising during the MIKSTRA study, which is favourable. According to sales statistics its use seems to have begun to decline nationally since then. However, while in the Pirkanmaa study macrolides were mainly used for lower respiratory tract infections, bronchitis (44%) and pneumonia (14%), in the 1998 MIKSTRA data pneumonia comprised only 5% and other LRTIs 31% of all indications for use of macrolides and half of them were used to treat otitis media or sinusitis. The situation has remained similar in the following years of MIKSTRA. From that point of view, development has proceeded in an undesirable direction as pneumonia is still the main indication for use of macrolides and it is recommended only as a secondary option for upper respiratory tract infections.

Use of macrolides could, however, be rather easily reduced by some 45–50%. Over eighty per cent of all macrolides in the MIKSTRA study were used to treat otitis media (29%), acute bronchitis (24%), sinusitis (21%) and unspecified URTI (9%) (Figure 17, page 77). The proportion of macrolides in the treatment of otitis media was 16% and in sinusitis 14% and this comprised together half of all macrolide use. At least one third of this could easily be replaced with other antibiotics, primarily with penicillin group. Another third of patients could probably avoid antibiotic all-together by improved diagnostics (Blomgren et al., 2004, Mäkelä & Leinonen, 1996, Palmu et al., 1999) or by a follow-up for one to three days from the onset of symptoms in the case of acute otitis media (Jensen & Lous, 1998, Marchetti et al., 2005, McCormick et al., 2005) and a week in the case of suspected sinusitis (de Bock et al., 2001, Gwaltney Jr, 2005c). This would mean already some 25–30% reduction in the total consumption of macrolides. In the case of acute bronchitis and unspecified URTI, which comprise one third of all macrolide use, the reduction could be even grater. A conservative estimate suggests that one third of these patients could avoid any antibiotic use and another third could be treated with penicillins or doxycycline instead of macrolides leading to approximately 20% additional reduction in the total consumption of macrolides.

Sulfa and sulfa-trimethoprim combinations are regarded as less desirable drugs in many countries because of the severe side-effects (Anonymous, 1995, Friis, 1987) or resistance (Kristinsson, 1999). It seems that sulfa-trimethoprim combinations are not used to treat respiratory tract infections in many other countries to the same extent as they are in Finland and Iceland. Sulfa-trimethoprim mixtures have a relatively pleasant taste to children, they are inexpensive, and often microbiologically justified. Severe side effects of sulfa-trimethoprim combinations have not been reported among children in Finland. A reasonable use of this antimicrobial combination for treating otitis media is not contradictory to the Finnish recommendations, but it is not recommended as a primary choice. Observations made in Iceland on the colonization of multiresistant strains of pneumococci in children after recurrent treatment with antibacterials, especially sulfa-trimethoprim combinations (Arason et al., 1996) warrants, however, cautiousness and close observation of the development of resistance also in our country. The declining use of this antimicrobial

94

combination is rather satisfying than worrying as it is not a recommended choice in uncomplicated UTIs either.

A high proportion of tetracyclines in total antibiotic use is not generally regarded as reflecting high quality prescribing at a European level because of the high level of resistance. In our data doxycycline was practically the only tetracycline prescribed in health centres. However, in the national sales data, roughly one third of all tetracyclines are other than doxycycline, but obviously they are prescribed by medical professionals other than GPs. Doxycycline can be regarded as even a recommendable choice in Finland in treating many respiratory tract infection in adults if the penicillin group cannot be used or if there is a suspicion of infections caused by *Mycoplasma* or *Chlamydia pneumoniae* (Korppi et al., 2003). The resistance of most respiratory pathogens to doxycycline is fairly low in Finland in contrast to already worrying high resistance levels to macrolides as well as sulfa-trimethoprim combinations, which are commonly used alternatives in these cases. It is possible that tetracyclines are used differently in Finland in respect to dosing and/or indication than in other countries having a high level of resistance.

Commercial information is an important modifier of the drug prescribing of practising doctors. Although the correctness of the information material is supervised by the authorities and it is usually not false as such, marketing may be unbalanced as a result of commercial interests and thereby direct prescribing practices in an inappropriate direction. A new product is launched by active marketing and competitors also need to respond to it. It is more profitable to put marketing efforts on new, more expensive drugs than old, less expensive alternatives. Commercial information is also product centred and does not, in most cases, deal with the patient's problem comprehensively. A probable explanation of the unnecessary increase in the use of amoxicillin with clavulanic acid is that it is marketed more actively than amoxicillin alone, which gives a false impression on the resistance situation and the status of this drug among other options. Penicillin-V again, is not a profitable substance from the point of view of pharmaceutical marketing, which leads to an unnecessary invisibility. Marketing of new macrolides for infections of the upper respiratory tract has been active and evidently successful from the industry's point of view.

Guidelines implementation

Antimicrobial use was at quite a satisfactory level in more ways than one already at the beginning of the MIKSTRA programme. For instance first-line drugs were chosen in 86% of cases of skin infections, 77% of streptococcal tonsillitis, and more than half of the cases of UTI (66%) and otitis media (62%). Recommendations on the duration of treatment were followed in 76% of cases of tonsillitis and more than half the cases of UTIs (55%). Ultrasonography had been

used in the diagnostics of most cases of sinusitis. Very significant changes could not be expected in such cases.

However, improvements in the quality of care were received during the implementation phase. In otitis media the use of the first-line recommended penicillin group increased only marginally but the duration of treatment approached the recommended significantly. The use of a first-line drug increased significantly in sinusitis, UTIs and, although still at a very low level, in acute bronchitis. Change towards the recommended duration of treatment was also significant in sinusitis and UTIs.

Five to seven days treatment is recommended in most respiratory tract infections. Half of the treatment courses with the first-line drug for otitis media and every seventh course for sinusitis were still unnecessarily long after the intervention. Shortening of courses is obviously the easiest, quickest and safest way of reducing individual patients' antibiotic burden, not to mention the economic savings that the patients most probably appreciate as well. Supervising of the pharmaceutical industry is essential to ensure that appropriate package sizes are available and that the treatment regimens and indications stated in the information material delivered by the industry are updated and in line with the CC-guidelines.

Although there were favourable changes in the quality of infection-specific use of antibiotics the proportion of patients who were prescribed antibiotics did not decrease in MIKSTRA's five-year follow-up. It is obvious that a change in the antibiotic choice or duration of treatment is much easier to carry out than to refrain from prescribing at all. On the other hand, our treatment guidelines do not emphasize a reduction of antibiotic consumption as such but rather focus on recommended antibiotic choices and the duration of treatment - except in the case of acute bronchitis. The prescribing of antibiotics for unspecified URTI was fairly restrictive in our study; only 7–12% of these patients received antibiotic treatment. The corresponding figures from other countries vary from 7% in Sweden (Andre et al., 2002, Stålsby Lundborg et al., 2002) to 18% for preschool children in Canada (Wang et al., 1999), and 38–48 % of children (Nash et al., 2002, Nyquist et al., 1998) and 28–51% of adults in the USA (Gonzales et al., 1997, Rubin et al., 2005). It is understandable that interventions focused on reducing antibiotic prescribing for URTIs yield more impressive results in countries like the USA compared to Finland given the starting points are so different.

That such a high proportion of patients with acute bronchitis were still prescribed antimicrobials was somewhat disappointing. Two thirds of the unnecessary prescribing of antibacterials in our study was for acute bronchitis. In the Pirkanmaa study both doctors and patients appeared to believe that acute bronchitis needs antimicrobial treatment, in spite of the fact that it contradicts official recommendations. This biased attitude is however not simply a Finnish problem (Gonzales & Sande, 1995, Gonzales et al., 2000, Little et al., 2005). In the marketing of antimicrobials, acute bronchitis is still mentioned as an equal indication among such infections as otitis media, sinusitis and pneumonia. This

may, in part, maintain doctors' wrong impression on the status of antimicrobials in the treatment of bronchitis. Repeatedly receiving antimicrobial prescriptions for acute bronchitis, for one, maintains patients' belief in this treatment option.

The concept of acute bronchitis is quite confusing and the existence of such an entity has even been questioned altogether (Hueston et al., 2000b). Acute bronchitis resembles closely URTI with cough but the clinical picture also shares some features with pneumonia. Attention should be paid to an accurate differential diagnosis to pneumonia, which is not simple. The diagnostic value of medical history and clinical findings in pneumonia are poor (Metlay et al., 1997). A chest x-ray can help to differentiate between pneumonia and bronchitis, but the sensitivity of routine chest x-ray is poor (Seppä et al., 2001). The usefulness of C-reactive protein and other inflammatory markers in assessment of the clinical condition of patients with LRTI have been contradictory (Babu et al., 1989, Flanders et al., 2004, Jonsson et al., 1997, van der Meer et al., 2005). It could be useful, however, in supporting viral aetiology and the non-prescribing of antibiotics with patients with prolonged symptoms of respiratory tract infection (Andre et al., 2004). If patients with pneumonia could be identified with sufficient sensitivity and specificity, then antibiotic treatment could be limited to these patients while those with no signs of pneumonia could then be diagnosed as having an unspecified URTI with cough and recognised as a viral disease and refrain from antibiotics. More research effort is still needed to clarify the diagnostic and treatment criteria of LRTI and to educate both doctors and the general population on the natural course of acute bronchitis.

The implementation of guidelines in MIKSTRA faced several unexpected problems: the tremendous turnover of doctors during the five years of the study in addition to the key person in the educational intervention falling seriously ill and being replaced only after a half-year break in the educational intervention. Consequently only just over a third of health centres realized the intervention program as recommended by the MIKSTRA research group. The heavy turnover of personnel in the health centres is an obvious problem for continuing medical education at the work site in general and it also undermines the importance of documenting the collectively agreed local practices.

In spite of all the problems of the intervention and the change of personnel there were measurable improvements in the quality of care. The effectiveness of the guideline implementation has in general been modest to moderate with a median effect of 6.0 to 14.1% (Grimshaw et al., 2004). Our result of a 6.4% improvement in the recommended prescribing for respiratory tract infections based on the intention-to-teat analysis is in line with these results. Subgroup-analyses are still needed to evaluate how much the implementation in MIKSTRA was undermined merely by the change of personnel.

The fact that the results in the study group health centres did not differ statistically from that of the control group health centres at follow-up may have several explanations. Firstly, it was regarded as unethical to delay publication and distribution of the national guidelines for five years, though publication may have contaminated the control group. Secondly the publicity of the program and

its results was an integral part of the implementation strategy. Thirdly, as ten of the originally willing 30 control health centres had to withdraw so late that they could not be replaced, the control group ended up to be somewhat biased in respect of prescribing compared to the study group health centres. In the circumstances, when the internal control setting in the study group health centres was lost, it would have been important to have collected base-line data from the control health centres, a procedure which was originally rejected thinking that it would have constituted an intervention and also been a source of contamination.

Antimicrobial treatment comprises less than ten per cent of the costs related to infections in the community while most of them are derived from the costs of sick leave and reconsultations (Jussila et al., 2005, Koskinen et al., 2004). The Current Care guidelines do not give much advice on these questions. The need for sick leave has to be, however, always assessed individually. More than by the infection diagnosis itself, the need is determined by the clinical condition of the patient and his/her occupation.

Some studies have discovered that patients' conception of his/her diagnosis and treatment may be quite different from that of the doctors (Britten et al., 2000, Jussila et al., 2005). This may lead to unrealistic expectations on the recovery which, when failing, readily leads to an unnecessary re-consultation (Macfarlane et al., 1997). Reassuring the patient on the benefit of a watchful waiting strategy in regard to the infection also demands listening and good communication (Barden et al., 1998, Little, 2005, Lundkvist et al., 2002). More attention should perhaps be paid on training doctors in communication skills as well as in making working conditions and workload such that they allow sufficient listening and discussion with the patients – in addition to the availability of proper diagnostic tools.

Diagnosing common respiratory tract infections in primary care is challenging and inevitably involves a lot of uncertainty. As a number of diagnostic tools have proved useful in defining between different options, these bedside diagnostic tools should be easily available in all health centres, with professionals properly trained in their use. Investment in tympanometries for all health posts treating children with infections and in training doctors and nurses how to use them, as well as the already existing ultrasound devices, would probably be recouped through a decreased number of false diagnoses of and unnecessary antibiotics for these infections. Moving to watchful waiting in otitis media and sinusitis and refraining from antibiotic prescription in acute bronchitis are significant changes in accustomed treatment practices in Finland. Both doctors and patients need time to adapt to the new way of thinking and tolerating uncertainty. However, antibiotics are too precious a medicine to be lost through seeking only marginal benefits.

CONCLUSIONS AND FUTURE CONSIDERATIONS

1. The data collection method, a one-page case-report form, proved to be straightforward, acceptable, and feasible for collecting data on the consultations for infections in primary care. It is obvious that infection-specific information on antibiotic use will also be needed in the future for monitoring the possible change in prescribing habits over time and updating the recommendations. As most health centres begin to be computerised, the possibility should be examined to collect corresponding data in future as a direct export from the electronic patient records. This could possibly be an integrated part of the national primary care database under development at the National Research and Development Centre for Welfare and Health, STAKES. Collecting data directly from electronic patient records would also allow the inclusion of the results of the diagnostic tests taken at the consultation, including those that are completed the following day or even later.

2. About one third of all out-of-hour consultations are due to infections. Respiratory tract infections comprise a major part of infections in primary care, except in patients aged >65 years, in whom urinary tract infections are the most common infection comprising one quarter of all infections. At younger age groups, upper respiratory tract infections are dominating while with increasing age, lower respiratory tract infections become more prominent. Most antibiotics are prescribed for respiratory tract infections, especially otitis media, sinusitis and acute bronchitis. Thus, when changes in total antibiotic use are needed, correct diagnosis and treatment of these infections should be focused on especially.

3. As symptoms and signs in respiratory tract infections are very similar, the key issue is how to differentiate between viral URTI and potential bacterial infections. According to this study, diagnostic tools were used quite often in sinusitis but not sufficiently to diagnose streptococcal tonsillitis. Tympanometry was used very seldom to diagnose otitis media, even in the one third of health centres that had the device, and C-reactive protein test was only seldom used before the decision was made to prescribe antibiotic for acute bronchitis. More focused interventions are needed to integrate the diagnostic tools that are regarded – according to current knowledge – as useful (sinus ultrasound, throat swab, tympanometry and CRP) in all health centres and to accustom the personnel to their use.

4. Despite the misfortune that the intervention process faced and the heavy turnover of personnel in the study health centres, which diluted the efficacy of the intervention, positive changes toward the new recommendations were found. The quality of antibiotic treatment increased especially in upper respiratory tract infections and UTI and the recommended diagnostic tools were used slightly more often after the intervention. Although positive changes in quality were found, the magnitude of change was modest in the intention-to-treat analysis. As half of the doctors changed during the programme, further subgroup analyses are needed to evaluate how much this undermined the effect of the implementation. Changing personnel should be taken into account in the future when designing interventions based on continuing medical education at the work site. Documentation of agreed-upon local practices is essential to be able to transmit the information on them to new and temporary workers.

5. The unchanged high prescribing of antibiotics for acute bronchitis was a disappointment. As this infection comprised the major part of the prescribing for indications where antibiotics are not recommended, strong efforts should be put in the future in educating both doctors and patients in the natural course of this disease and the futility of antibiotics in its treatment.

6. According to this study, macrolides are used very often as first-line drugs to treat upper respiratory tract infections and acute bronchitis without special justification. Macrolides are important drugs, needed especially for the treatment of community acquired pneumonia. The proportion of macrolide resistant pneumococci has climbed to a level that already seems to be a threat to patient safety. In order to preserve the effect of macrolides in pneumonia their use in other respiratory tract infections should be drastically reduced. A targeted campaign is needed to introduce the idea that whenever a macrolide is selected for use instead of other options for upper respiratory tract infections or bronchitis in outpatient care, there has to be a sound justification for it.

ACKNOWLEDGEMENTS

REFERENCES

Adams, P.F., Hendershot, G.E. & Marano, M.A. (1999) Current estimates from the National Health Interview Survey, 1996.*Vital Health Statistics 10* (Hyattsville, Maryland, National Center for Health Statistics, Centers for Disease Control and Prevention).

Ala-Fossi, N. (1997) Uuden lääkkeen diffuusio yleislääkäreiden ja gynekologien keskuudessa (Diffusion of a new drug among GPs and gynaecologists) (in Finnish). *Dosis* 4-10.

Albrich, W.C., Monnet, D.L. & Harbarth, S. (2004) Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. *Emerg Infect Dis* 10:514-517.

Alho, O.P., Koivu, M., Sorri, M. & Rantakallio, P. (1991) The occurrence of acute otitis media in infants. A life-table analysis. *Int J Pediatr Otorhinolaryngol* 21:7-14.

Andre, M., Odenholt, I., Schwan, A., Axelsson, I., Eriksson, M., Hoffman, M., Mölstad, S., Runehagen, A., Stålsby Lundborg, C. & Wahlstrom, R. (2002) Upper respiratory tract infections in general practice: diagnosis, antibiotic prescribing, duration of symptoms and use of diagnostic tests. *Scand J Infect Dis* 34:880-886.

Andre, M., Schwan, A. & Odenholt, I. (2004) The use of CRP tests in patients with respiratory tract infections in primary care in Sweden can be questioned. *Scand J Infect Dis* 36:192-197.

Anonymous (1995) Co-trimoxazole use restricted. *Drug Ther Bull* 33:92-93.

Arason, V., Sigurdsson, J., Kristinsson, K., Getz, L. & Gudmundsson, S. (2005) Otitis media, tympanostomy tube placement, and use of antibiotics. *Scand J Prim Health Care* 23:184-191.

Arason, V.A., Kristinsson, K.G., Sigurdsson, J.A., Stefansdottir, G., Molstad, S. & Gudmundsson, S. (1996) Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 313:387-391.

Arinen, S., Häkkinen, U., Klaukka, T., Klavus, J., Lehtonen, R. & Aro, S. (1998) Suomalaisten terveys ja terveyspalvelujen käyttö/Health and use of health services in Finland.*Official Statistics of Finland Terveys/Health care 5* (Helsinki, STAKES, KELA).

Armstrong, G.L.M.D. & Pinner, R.W.M.D. (1999) Outpatient Visits for Infectious Diseases in the United States, 1980 Through 1996. *Archives of Internal Medicine* 159:2531-2536.

Aromaa, A. & Koskinen, S. (2002) Terveys ja toimintakyky Suomessa Terveys 2000 - tutkimuksen perustulokset (Health and functional capacity in Finland. Baseline results of the Health 2000 health examination survey) (in Finnish) in: Kansanterveyslaitos (Ed) *Kansanterveyslaitoksen julkaisuja B* (Helsinki, Kansanterveyslaitos).

Ashworth, M., Charlton, J., Ballard, K., Latinovic, R. & Gulliford, M. (2005) Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. *Br J Gen Pract* 55:603-608.

Ashworth, M., Latinovic, R., Charlton, J., Cox, K., Rowlands, G. & Gulliford, M. (2004) Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *J Public Health (Oxf)* 26:268-274.

Austin, D.J., Kristinsson, K.G. & Anderson, R.M. (1999) The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci U S A* 96:1152-1156.

Avorn, J. & Soumerai, S.B. (1983) Improving drug-therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing". *N Engl J Med* 308:1457-1463.

Axelsson, A., Grebelius, N., Chidekel, N. & Jensen, C. (1970) The correlation between the radiological examination and the irrigation findings in maxillary sinusitis. *Acta Otolaryngol* 69:302-306.

Babu, G., Ganguly, N.K., Singhi, S. & Walia, B.N. (1989) Value of C-reactive protein concentration in diagnosis and management of acute lower respiratory infections. *Trop Geogr Med* 41:309-315.

Bakteerien lääkeresistenssin torjuminen ja mikrobilääkepolitiikan kehittäminen - työryhmä (2000) Bakteerien lääkeresistenssin torjuminen ja mikrobilääkepolitiikan kehittäminen (Fighting bacterial resistance to antibiotics and developing antibiotic policy) (in Finnish with English summary) in: Sosiaali- ja terveysministeriö (Ed) *Työryhmämuistioita* (Helsinki, Sosiaali- ja terveysministeriö).

Baquero, F. (1999) Evolving resistance patterns of Streptococcus pneumoniae: a link with long-acting macrolide consumption? *J Chemother* 11 Suppl 1:35-43.

Barden, L.S., Dowell, S.F., Schwartz, B. & Lackey, C. (1998) Current attitudes regarding use of antimicrobial agents: results from physician's and parents' focus group discussions. *Clin Pediatr (Phila)* 37:665-671.

Bent, S., Nallamothu, B.K., Simel, D.L., Fihn, S.D. & Saint, S. (2002) Does this woman have an acute uncomplicated urinary tract infection? *JAMA* 287:2701-2710.

Berg, O., Carenfelt, C., Rystedt, G. & Ånggård, A. (1986) Occurrence of asymptomatic sinusitis in common cold and other acute ENT-infections. *Rhinology* 24:223-225.

Bergman, M., Huikko, S., Pihlajamäki, M., Laippala, P., Palva, E., Huovinen, P., Seppälä, H. & Finnish Study Group for Antimicrobial, R. (2004) Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997-2001. *Clin Infect Dis* 38:1251-1256.

Bernard, P., Bedane, C., Mounier, M., Denis, F., Catanzano, G. & Bonnetblanc, J.M. (1989) Streptococcal cause of erysipelas and cellulitis in adults. A microbiologic study using a direct immunofluorescence technique. *Arch Dermatol* 125:779-782.

Birnbaum, H.G., Morley, M., Greenberg, P.E. & Colice, G.L. (2002) Economic burden of respiratory infections in an employed population. *Chest* 122:603-611.

Bisno, A.L., Gerber, M.A., Gwaltney, J.M., Jr., Kaplan, E.L. & Schwartz, R.H. (2002) Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. *Clin Infect Dis* 35:113-125.

Bisno, A.L. & Stevens, D.L. (1996) Streptococcal infections of skin and soft tissues. *N Engl J Med* 334:240-245.

Blomgren, K., Alho, O.-P., Ertama, L., Huovinen, P., Korppi, M., Mäkelä, M., Penttilä, M., Pitkäranta, A., Savolainen, S., Varonen, H. & Suonpää, J. (2005) Acute sinusitis: Finnish clinical practice guidelines. *Scand J Infect Dis* 37:245-250.

Blomgren, K., Hytönen, M., Pellinen, J., Relander, M. & Pitkäranta, A. (2002) Diagnostic accuracy of acute maxillary sinusitis in adults in primary care. *Scand J Prim Health Care* 20:40-44.

Blomgren, K. & Pitkäranta, A. (2003) Is it possible to diagnose acute otitis media accurately in primary health care? *Fam Pract* 20:524-527.

Blomgren, K. & Pitkäranta, A. (2005) Current challenges in diagnosis of acute otitis media. *Int J Pediatr Otorhinolaryngol* 69:295-299.

Blomgren, K., Pohjavuori, S., Poussa, T., Hatakka, K., Korpela, R. & Pitkäranta, A. (2004) Effect of accurate diagnostic criteria on incidence of acute otitis media in otitis-prone children. *Scand J Infect Dis* 36:6-9.

Bradley, C.P. (1992a) Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners. *Br J Gen Pract* 42:454-458.

Bradley, C.P. (1992b) Uncomfortable prescribing decisions: a critical incident study. *BMJ* 304:294-296.

Britten, N., Stevenson, F.A., Barry, C.A., Barber, N. & Bradley, C.P. (2000) Misunderstandings in prescribing decisions in general practice: qualitative study. *BMJ* 320:484-488.

Brody, D.S., Miller, S.M., Lerman, C.E., Smith, D.G., Lazaro, C.G. & Blum, M.J. (1989) The relationship between patients' satisfaction with their physicians and perceptions about interventions they desired and received. *Med Care* 27:1027-1035.

Bronzwaer, S.L., Cars, O., Buchholz, U., Molstad, S., Goettsch, W., Veldhuijzen, I.K., Kool, J.L., Sprenger, M.J. & Degener, J.E. (2002) A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerg Infect Dis* 8:278-282.

Bruinsma, N., Hutchinson, J.M., van den Bogaard, A.E., Giamarellou, H., Degener, J. & Stobberingh, E.E. (2003) Influence of population density on antibiotic resistance. *J Antimicrob Chemother* 51:385-390.

Bruinsma, N., Kristinsson, K.G., Bronzwaer, S., Schrijnemakers, P., Degener, J., Tiemersma, E., Hryniewicz, W., Monen, J., Grundmann, H. & on behalf of EARSS participants (2004) Trends of penicillin and erythromycin resistance among invasive Streptococcus pneumoniae in Europe. *J Antimicrob Chemother* 54:1045-1050.

Burgers, J.S., Grol, R., Klazinga, N.S., Makela, M. & Zaat, J. (2003) Towards evidence-based clinical practice: an international survey of 18 clinical guideline programs. *Int J Qual Health Care* 15:31-45.

Butler, C.C., Rollnick, S., Pill, R., Maggs-Rapport, F. & Stott, N. (1998) Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 317:637-642.

Cabana, M.D., Rand, C.S., Powe, N.R., Wu, A.W., Wilson, M.H., Abboud, P.A. & Rubin, H.R. (1999) Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 282:1458-1465.

Carbon, C., Cars, O. & Christiansen, K. (2002) Moving from recommendation to implementation and audit: part 1. Current recommendations and programs: a critical commentary. *Clin Microbiol Infect* 8 Suppl 2:92-106.

Cars, O. (2001) The hidden impact of antibacterial resistance in respiratory tract infection. Steering an appropriate course: principles to guide antibiotic choice. *Respir Med* 95 Suppl A:S20-25; discussion S26-27.

Cars, O. & Ekdahl, K. (Eds.) (2003) SWEDRES 2002. A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine. The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) and the Swedish Institute for Infectious Disease Control, Uppsala.

Cars, O., Mölstad, S. & Melander, A. (2001) Variation in antibiotic use in the European Union. *Lancet* 357:1851-1853.

Cars, O. & Olsson-Liljequist, B. (Eds.) (2005) SWEDRES 2004. A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine. The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) and the Swedish Institute for Infectious Disease Control, Malmö.

Cartwright, F.F. & Biddiss, M. (2000) Disease and History. Sutton Publishing Limited, Gloucestershire.

Centers for Disease Control and Prevention (2005) Infectious Disease and Dermatologic Conditions in Evacuees and Rescue Workers After Hurricane Katrina--Multiple States, August-September, 2005. *JAMA* 294:2158-2160.

Chalmers, I., Dickersin, K. & Chalmers, T.C. (1992) Getting to grips with Archie Cochrane's agenda. *BMJ* 305:786-788.

Chang, E.T., Smedby, K.E., Hjalgrim, H., Schöllkopf, C., Porwit-MacDonald, A., Sundström, C., Tani, E., d'Amore, F., Melbye, M., Adami, H.-O. & Glimelius, B. (2005) Medication Use and Risk of Non-Hodgkin's Lymphoma. *American Journal of Epidemiology* 162:965-974.

Christakis, D.A., Zimmerman, F.J., Wright, J.A., Garrison, M.M., Rivara, F.P. & Davis, R.L. (2001) A randomized controlled trial of point-of-care evidence to improve the antibiotic prescribing practices for otitis media in children. *Pediatrics* 107:E15.

Coenen, S., Van Royen, P., Michiels, B. & Denekens, J. (2004) Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. *J Antimicrob Chemother* 54:661-672.

Cohen, M.L. (1992) Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science* 257:1050-1055.

Conly, J. (2002) Antimicrobial resistance in Canada. *CMAJ* 167:885-891.

Consensus statement (1997) Antibioottiresistenssi; Säilyykö lääkkeiden teho? (Antibiotic resistance; Will medicines remain effective?) (in Finnish). *Antibioottiresistenssi; Säilyykö lääkkeiden teho?* (Hanasaari).

de Bock, G.H., van Erkel, A.R., Springer, M.P. & Kievit, J. (2001) Antibiotic prescription for acute sinusitis in otherwise healthy adults. Clinical cure in relation to costs. *Scand J Prim Health Care* 19:58-63.

De Sutter, A.I., De Meyere, M.J., De Maeseneer, J.M. & Peersman, W.P. (2001) Antibiotic prescribing in acute infections of the nose or sinuses: a matter of personal habit? *Fam Pract* 18:209-213.

Del Mar, C., Glasziou, P. & Spinks, A. (2004).Antibiotics for sore throat. *The Cochrane Database of Systematic Reviews 2004,* http://www.thecochranelibrary.com, February 2006

Dobbs, F. (1996) A scoring system for predicting group A streptococcal throat infection. *Br J Gen Pract* 46:461-464.

Dollman, W.B., LeBlanc, V.T., Stevens, L., O'Connor, P.J. & Turnidge, J.D. (2005) A community-based intervention to reduce antibiotic use for upper respiratory tract infections in regional South Australia. *Med J Aust* 182:617-620.

Donowitz, G.R. & Mandell, G.L. (1988) Beta-lactam antibiotics. *N Engl J Med* 318:419-426.

Donowitz, G.R. & Mandell, G.L. (2005) Acute pneumonia, in: *Mandell, Douglas, and Bennett's Principles and practice of infectious diseases*, Vol., pp. 819-845. Elsevier Curchill Livingstone Inc.,

Dunais, B., Pradier, C., Carsenti, H., Sabah, M., Mancini, G., Fontas, E. & Dellamonica, P. (2003) Influence of child care on nasopharyngeal carriage of Streptococcus pneumoniae and Haemophilus influenzae. *Pediatr Infect Dis J* 22:589-592.

Ebell, M.H.M.D., Smith, M.A.M.D., Barry, H.C.M.D., Ives, K.B.S. & Carey, M.B.S. (2000) Does This Patient Have Strep Throat? *JAMA* 284:2912-2918.

Ekedahl, A., Andersson, S.I., Hovelius, B., Mölstad, S., Liedholm, H. & Melander, A. (1995) Drug prescription attitudes and behaviour of general practitioners. Effects of a problem-oriented educational programme. *Eur J Clin Pharmacol* 47:381-387.

Emborg, h.D., Heuer, O.E. & Larsen, P.B. (Eds.) (2005) DANMAP 2004. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Danmark. Danish Institute for Food and Veterinary Research, Soborg.

Enne, V.I., Livermore, D.M., Stephens, P. & Hall, L.M. (2001) Persistence of sulphonamide resistance in Escherichia coli in the UK despite national prescribing restriction. *Lancet* 357:1325-1328.

European Union Conference 'The Microbial Threat' (1998).The Copenhagen Recommendation. http://www.tours.inra.fr/urbase/internet/resultats/antibioresistance/copen2.htm,

Fahey, T., Smucny, J., Becker, L. & Glazier, R. (2004).Antibiotics for acute bronchitis. *The Cochrane Database of Systematic Reviews,* http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000245/frame.html, 23.11. 2005

Fahey, T., Stocks, N. & Thomas, T. (1998) Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 316:906-910.

Fendrick, A.M.M.D., Monto, A.S.M.D., Nightengale, B.P. & Sarnes, M.P. (2003) The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med* 163:487-494.

Finitzo, T., Friel-Patti, S., Chinn, K. & Brown, O. (1992) Tympanometry and otoscopy prior to myringotomy: issues in diagnosis of otitis media. *Int J Pediatr Otorhinolaryngol* 24:101-110.

Finkelstein, J.A., Stille, C., Nordin, J., Davis, R., Raebel, M.A., Roblin, D., Go, A.S., Smith, D., Johnson, C.C., Kleinman, K., Chan, K.A. & Platt, R. (2003) Reduction in antibiotic use among US children, 1996-2000. *Pediatrics* 112:620-627.

Flanders, S.A., Stein, J., Shochat, G., Sellers, K., Holland, M., Maselli, J., Drew, W.L., Reingold, A.L. & Gonzales, R. (2004) Performance of a bedside c-reactive protein test in the diagnosis of community-acquired pneumonia in adults with acute cough. *Am J Med* 116:529-535.

Fleming, D.M., Ross, A.M., Cross, K.W. & Kendall, H. (2003) The reducing incidence of respiratory tract infection and its relation to antibiotic prescribing. *Br J Gen Pract* 53:778-783.

Fleming, D.M., Ross, A.M., Cross, K.W., Kendall, H. & Elliot, A.J. (2005) Concerning: 'Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database'. *J Public Health (Oxf)* 27:228-229; author reply 229-231.

Forssell, G., Hakansson, A. & Mansson, N.O. (2001) Risk factors for respiratory tract infections in children aged 2-5 years. *Scand J Prim Health Care* 19:122-125.

Fox, J.P., Hall, C.E., Cooney, M.K., Luce, R.E. & Kronmal, R.A. (1972) The Seattle virus watch II. Objectives, study population and its observation, data processing and summary of illnesses. *Am J Epidemiol* 96:270-285.

Friis, H. (1987) Sulfa med trimetoprim - en farlig kombination (Sulfa with trimethoprim - a dangerous combination) (in Danish). *Ugeskr Laeger* 149:98-100.

Glasziou, P.P., Del Mar, C.B., Sanders, S.L. & Hayem, M. (2004).Antibiotics for acute otitis media in children. *The Cochrane Database of Systematic Reviews,* http://www.thecochranelibrary.com, August 2005

Gonzales, R., Barrett, P.H., Jr., Crane, L.A. & Steiner, J.F. (1998) Factors associated with antibiotic use for acute bronchitis. *J Gen Intern Med* 13:541-548.

Gonzales, R. & Sande, M. (1995) What will it take to stop physicians from prescribing antibiotics in acute bronchitis? *Lancet* 345:665-666.

Gonzales, R., Steiner, J.F., Lum, A. & Barrett, P.H., Jr. (1999) Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. *JAMA* 281:1512-1519.

Gonzales, R., Steiner, J.F., Maselli, J., Lum, A. & Barrett, P.H., Jr. (2001) Impact of reducing antibiotic prescribing for acute bronchitis on patient satisfaction. *Eff Clin Pract* 4:105-111.

Gonzales, R., Steiner, J.F. & Sande, M.A. (1997) Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 278:901-904.

Gonzales, R., Wilson, A., Crane, L.A. & Barrett, P.H., Jr. (2000) What's in a name? Public knowledge, attitudes, and experiences with antibiotic use for acute bronchitis. *Am J Med* 108:83-85.

Goossens, H., Ferech, M., Vander Stichele, R., Elseviers, M. & ESAC Project Group (2005) Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 365:579-587.

Green, L.A., Culpepper, L., de Melker, R.A., Froom, J., van Balen, F., Grob, P. & Heeren, T. (2000) Tympanometry interpretation by primary care physicians. A report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN). *J Fam Pract* 49:932-936.

Grimshaw, J.M., Thomas, R.E., MacLennan, G., Fraser, C., Ramsay, C.R., Vale, L., Whitty, P., Eccles, M.P., Matowe, L., Shirran, L., Wensing, M., Dijkstra, R. & Donaldson, C. (2004) Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 8:1-351.

Guillemot, D., Carbon, C., Balkau, B., Geslin, P., Lecoeur, H., Vauzelle-Kervroedan, F., Bouvenot, G. & Eschwege, E. (1998) Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. *JAMA* 279:365-370.

Gwaltney Jr, J.M. (1994) Computed tomographic study of the common cold. *N Engl J Med* 330:25-30.

Gwaltney Jr, J.M. (2005a) Acute Bronchitis, in: *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, Vol., pp. 803-806. Elsevier, Philadelphia.

Gwaltney Jr, J.M. (2005b) The Common cold, in: *Mandell, Douglas, and Bennett's Principles and practice of infectious diseases*, Vol., pp. 747-752. Elsevier Curchill Livingstone Inc.,

Gwaltney Jr, J.M. (2005c) Sinusitis, in: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, Vol., pp. 772-783. Elsevier, Philadelphia.

Hagman, E. (1981) Avohoidon sairauspanoraama (Disease panorama in outpatient care) (in Finnish). *Suomen Lääkärilehti* 36:735-739.

Hamm, R.M., Hicks, R.J. & Bemben, D.A. (1996) Antibiotics and respiratory infections: are patients more satisfied when expectations are met? *J Fam Pract* 43:56-62.

Hay, A.D., Thomas, M., Montgomery, A., Wetherell, M., Lovering, A., McNulty, C., Lewis, D., Carron, B., Henderson, E. & MacGowan, A. (2005) The relationship between primary care antibiotic prescribing and bacterial resistance in adults in

the community: a controlled observational study using individual patient data. *J Antimicrob Chemother* 56:146-153.

Hemminki, E., Forsman, H. & Hemminki, K. (1974) Prescription of antimicrobial drugs by general practitioners. *Infection* 2:203-206.

Hennessy, T.W., Petersen, K.M., Bruden, D., Parkinson, A.J., Hurlburt, D., Getty, M., Schwartz, B. & Butler, J.C. (2002) Changes in antibiotic-prescribing practices and carriage of penicillin-resistant Streptococcus pneumoniae: A controlled intervention trial in rural Alaska. *Clin Infect Dis* 34:1543-1550.

Herruzo, R., Chamorro, L., Garcia, M.E., Gonzalez, M.C., Lopez, A.M., Mancenido, N. & Yebenes, L. (2002) Prevalence and antimicrobial-resistance of S. pneumoniae and S. pyogenes in healthy children in the region of Madrid. *Int J Pediatr Otorhinolaryngol* 65:117-123.

Heuer, O.E. & Larsen, P.B. (Eds.) (2004) DANMAP 2003. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. Danish Institute for Food and Veterinary Research, Soborg.

Himmel, W., Lippert-Urbanke, E. & Kochen, M.M. (1997) Are patients more satisfied when they receive a prescription? The effect of patient expectations in general practice. *Scand J Prim Health Care* 15:118-122.

Holmberg, H., Bodin, L., Jonsson, I. & Krook, A. (1990) Rapid aetiological diagnosis of pneumonia based on routine laboratory features. *Scand J Infect Dis* 22:537-545.

Honkanen, P.O., Herva, E., Kujala, P., Leinonen, M., Lähde, S., Mäkelä, M., Rautakorpi, U.-M. & Tukiainen, H. (1999) Äkillisen keuhkoputkitulehduksen hoitosuositus (Acute bronchitis: Finnish clinical practice guidelines) (in Finnish). *Duodecim* 115:2171-2175.

Hopstaken, R.M., Muris, J.W., Knottnerus, J.A., Kester, A.D., Rinkens, P.E. & Dinant, G.J. (2003) Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract* 53:358-364.

Hopstaken, R.M., Stobberingh, E.E., Knottnerus, J.A., Muris, J.W.M., Nelemans, P., Rinkens, P.E.L.M. & Dinant, G.J. (2005) Clinical items not helpful in differentiating viral from bacterial lower respiratory tract infections in general practice. *J Clin Epidemiol* 58:175-183.

House of Lords Selected Commitee on Science and Technology (1998).Resistance to Antibiotics and Other Microbial Agents. *Science and Technology Committee Reports,* http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/081vii/st0701.htm, October 2005

Howard, J.E., Nelson, J.D., Clahsen, J. & Jackson, L.H. (1976) Otitis media of infancy and early childhood. A double-blind study of four treatment regimens. *Am J Dis Child* 130:965-970.

Howie, J.G. (1983) Some non-bacteriological determinants and implications of antibiotic use in upper respiratory tract illness. *Scand J Infect Dis Suppl* 39:68-72.

Huang, S.S., Finkelstein, J.A., Rifas-Shiman, S.L., Kleinman, K. & Platt, R. (2004) Community-Level Predictors of Pneumococcal Carriage and Resistance in Young Children. *Am. J. Epidemiol.* 159:645-654.

Hueston, W.J., Jenkins, R. & Mainous, A.G., 3rd (2000a) Does drug treatment of patients with acute bronchitis reduce additional care seeking? Evidence from the Practice Partner Research Network. *Arch Fam Med* 9:997-1001.

Hueston, W.J., Mainous, A.G., 3rd, Dacus, E.N. & Hopper, J.E. (2000b) Does acute bronchitis really exist? A reconceptualization of acute viral respiratory infections. *J Fam Pract* 49:401-406.

Hueston, W.J. & Slott, K. (2000) Improving quality or shifting diagnoses? What happens when antibiotic prescribing is reduced for acute bronchitis? *Arch Fam Med* 9:933-935.

Huovinen, P. & Klaukka, T. (1991) Erytromysiinin käyttöä vähennettävä (The use of erythromycin must be reduced) (in Finnish). *Suomen Lääkärilehti* 46:3241.

Huovinen, P. & Vaara, M. (Eds.) (1995) Kapseli 24; Avohoidon mikrobilääkkeet (Antimicrobial agents in outpatient care) (in Finnish). Lääkelaitos ja Kansaneläkelaitos, Forssa.

Hutchinson, J.M., Jelinski, S., Hefferton, D., Desaulniers, G. & Parfrey, P.S. (2001) Role of diagnostic labeling in antibiotic prescription. *Can Fam Physician* 47:1217-1224.

Hux, J.E., Melady, M.P. & DeBoer, D. (1999) Confidential prescriber feedback and education to improve antibiotic use in primary care: a controlled trial. *CMAJ* 161:388-392.

Hyde, T.B., Gay, K., Stephens, D.S., Vugia, D.J., Pass, M., Johnson, S., Barrett, N.L., Schaffner, W., Cieslak, P.R., Maupin, P.S., Zell, E.R., Jorgensen, J.H., Facklam, R.R. & Whitney, C.G. (2001) Macrolide resistance among invasive Streptococcus pneumoniae isolates. *JAMA* 286:1857-1862.

Idänpään-Heikkilä, J. (1979) Data collection in Finland, in: *Studies in drug utilization*, Vol., pp. 35-48. WHO Regional Office for Europe, Copenhagen.

Ikäheimo, R., Uhari, M., Lumio, J., Huovinen, P., Lipponen, P., Kouri, T., Ruutu, M. & Louhioja, T. (2000) Virtsatieinfektiot (Urinary tract infections; Finnish clinical practice guidelines) (in Finnish). *Duodecim* 116:782-796.

Jacobs, M.R., Felmingham, D., Appelbaum, P.C., Gruneberg, R.N. & the Alexander Project Group (2003) The Alexander Project 1998-2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J. Antimicrob. Chemother.* 52:229-246.

Jensen, P.M. & Lous, J. (1998) Antibiotic treatment of acute otitis media. Criteria and performance in Danish general practice. *Scand J Prim Health Care* 16:18-23.

Johansen, E.C., Lildholdt, T., Damsbo, N. & Eriksen, E.W. (2000) Tympanometry for diagnosis and treatment of otitis media in general practice. *Fam Pract* 17:317-322.

Joki-Erkkilä, V.P., Pukander, J. & Laippala, P. (2000) Alteration of clinical picture and treatment of pediatric acute otitis media over the past two decades. *Int J Pediatr Otorhinolaryngol* 55:197-201.

Jonsson, J.S., Sigurdsson, J.A., Kristinsson, K.G., Guthnadottir, M. & Magnusson, S. (1997) Acute bronchitis in adults. How close do we come to its aetiology in general practice? *Scand J Prim Health Care* 15:156-160.

Jussila, M., Sintonen, H., Koivula, I. & Lumio, J. (2005) Hengitystieinfektioiden hoito terveyskeskuksessa - potilaan, lääkärin ja yhteiskunnan näkökulma (The treatment of respiratory tract infections in primary health care: The view of the patient, the doctor and society) (in Finnish with English abstract). *Suomen Lääkärilehti* 60:2577-2582.

Juven, T., Ruuskanen, O. & Mertsola, J. (2003) Symptoms and signs of community-acquired pneumonia in children. *Scand J Prim Health Care* 21:52-56.

Karma, P.H., Penttilä, M.A., Sipilä, M.M. & Kataja, M.J. (1989) Otoscopic diagnosis of middle ear effusion in acute and non-acute otitis media. I. The value of different otoscopic findings. *Int J Pediatr Otorhinolaryngol* 17:37-49.

Kastner, U. & Guggenbichler, J.P. (2001) Influence of macrolide antibiotics on promotion of resistance in the oral flora of children. *Infection* 29:251-256.

Kay, N.J., Setia, R.N. & Stone, J. (1984) Relevance of conventional radiography in indicating maxillary antral lavage. *Ann Otol Rhinol Laryngol* 93:37-38.

Kilkkinen, A., Pietinen, P., Klaukka, T., Virtamo, J., Korhonen, P. & Adlercreutz, H. (2002) Use of oral antimicrobials decreases serum enterolactone concentration. *Am J Epidemiol* 155:472-477.

Klaukka, T. & Rautakorpi, U.-M. (1995) Mikrobilääkkeiden lääke-esittelyt Pirkanmaalla (Visit of pharmaceutical sales representatives related to antimicrobials in Pirkanmaa) (in Finnish). *Suomen Lääkärilehti* 50:2451-2453.

Knekt, P., Adlercreutz, H., Rissanen, H., Aromaa, A., Teppo, L. & Heliovaara, M. (2000) Does antibacterial treatment for urinary tract infection contribute to the risk of breast cancer? *Br J Cancer* 82:1107-1110.

Koivula, I., Korppi, M., Kärkkäinen, U., Perola, O., Lahti, E., Ruuskanen, O., Rantala, M., Hakanen, a., Jalava, J. & Huovinen, P. (2004) Vakavat pneumokokki-infektiot ja epäonnistunut makrolidihoito (Severe pneumococcal infections and treatment failure with macrolides) (in Finnish). *Suomen Lääkärilehti* 59:2262-2264.

Kokko, S. (1988) Tauti ja sairaus - työikäiset terveyskeskuslääkärin vastaanotolla (Disease and illness - working-aged patients consulting GPs) (in Finnish). Academic Dissertation (University of Kuopio).

Korppi, M., Koivula, I. & Jokinen, C. (2003) Alahengitystieinfektiot (Lower respiratory tract infections) (in Finnish), in: *Mikrobiologia ja infektiosairaudet*, Vol., pp. 374-388. Kustannus Oy Duodecim, Helsinki.

Koskinen, H., Rautakorpi, U.-M., Mäkelä, M., Sintonen, H. & MIKSTRA Collaborative Study Group (2004) Cost-effectiveness of treating acute otitis media in children: Implementing Current Care -guidelines. *WONCA Europe Regional Conference 2004* (Amsterdam).

Kozyrskyj, A.L., Carrie, A.G., Mazowita, G.B., Lix, L.M., Klassen, T.P. & Law, B.J. (2004) Decrease in antibiotic use among children in the 1990s: not all antibiotics, not all children. *CMAJ* 171:133-138.

Kristinsson, K.G. (1995) Epidemiology of penicillin resistant pneumococci in Iceland. *Microb Drug Resist* 1:121-125.

Kristinsson, K.G. (1997) Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Microb Drug Resist* 3:117-123.

Kristinsson, K.G. (1999) Modification of prescribers' behavior: the Icelandic approach. *Clin Microbiol Infect* 5(Suppl 4):S43 -47.

Kristo, A., Uhari, M., Luotonen, J. & et al. (2003) Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. *Pediatrics* 111:586-589.

Lahnajärvi, L., Klaukka, T. & Enlund, H. (1997) Ahvenanmaa - itsehallittua lääkekulutusta (The Åland Islands - autonous pharmaceutical consumption) (in Finnish with English summary) in: Kansaneläkelaitos (Ed) *Sosiaali- ja terveysturvan tutkimuksia 23* (Helsinki, Kansaneläkelaitos).

Laine, K., Määttä, T., Varonen, H. & Mäkelä, M. (1998) Diagnosing acute maxillary sinusitis in primary care: a comparison of ultrasound, clinical examination and radiography. *Rhinology* 36:2-6.

Lauslahti, K., Klaukka, T., Mäkelä, M., Nikkarinen, T., Palva, E., Rautakorpi, U.-M. & Huovinen, P. (1998) MIKSTRA ohjaamaan avohoidon mikrobilääkitystä (MIKSTRA to guide outpatient antibiotic use) (in Finnish). *Suomen Lääkärilehti* 53:1524-1526.

Leistevuo, J., Huikko, S., Rautakorpi, U.-M., Leistevuo, T., Honkanen, P., Klaukka, T., Mäkelä, M., Palva, E., Roine, R., Sarkkinen, H., Varonen, H., Huovinen, P. & The MIKSTRA Collaborative Study Group (2005) Prescription rates and diagnostic patterns are stable: A comparison of high-, medium- and low-

prescribing primary care physicians treating community-acquired respiratory tract infections. *Scand J Infect Dis* 37:465-470.

Leistevuo, T., Österblad, M., Toivonen, P., Kahra, A., Lehtonen, A. & Huovinen, P. (1996) Colonization of resistant faecal aerobic gram-negative bacilli among geriatric patients in hospital and the community. *J Antimicrob Chemother* 37:169-173.

Little, P. (2005) Delayed prescribing of antibiotics for upper respiratory tract infection. *BMJ* 331:301-302.

Little, P., Gould, C., Williamson, I., Warner, G., Gantley, M. & Kinmonth, A.L. (1997) Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 315:350-352.

Little, P., Rumsby, K., Kelly, J., Watson, L., Moore, M., Warner, G., Fahey, T. & Williamson, I. (2005) Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: A randomized controlled trial. *JAMA* 293:3029-3035.

Livermore, D.M. (2005) Minimising antibiotic resistance. *The Lancet Infectious Diseases* 5:450-459.

Logan, R.L. & Scott, P.J. (1996) Uncertainty in clinical practice: implications for quality and costs of health care. *Lancet* 347:595-598.

Lumio, J. (1996) Montako antibioottia terveyskeskuslääkäri tarvitsee? (How many antibiotics does a GP need?) (in Finnish). *Suomen Lääkärilehti* 51:3133-3135.

Lundborg, C.S., Wahlstrom, R., Oke, T., Tomson, G. & Diwan, V.K. (1999) Influencing prescribing for urinary tract infection and asthma in primary care in Sweden: a randomized controlled trial of an interactive educational intervention. *J Clin Epidemiol* 52:801-812.

Lundkvist, J., Åkerlind, I., Borgquist, L. & Mölstad, S. (2002) The more time spent on listening, the less time spent on prescribing antibiotics in general practice. *Fam Pract* 19:638-640.

Macfarlane, J., Holmes, W., Gard, P., Macfarlane, R., Rose, D., Weston, V., Leinonen, M., Saikku, P. & Myint, S. (2001) Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 56:109-114.

Macfarlane, J., Holmes, W., Gard, P., Thornhill, D., Macfarlane, R. & Hubbard, R. (2002) Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. *BMJ* 324:91-94.

Macfarlane, J., Prewett, J., Rose, D., Gard, P., Cunningham, R., Saikku, P., Euden, S. & Myint, S. (1997) Prospective case-control study of role of infection in patients who reconsult after initial antibiotic treatment for lower respiratory tract infection in primary care. *BMJ* 315:1206-1210.

MacKay, D.N. (1996) Treatment of acute bronchitis in adults without underlying lung disease. *J Gen Intern Med* 11:557-562.

Mäkelä, M. (1989) Effect of latex agglutination test on prescribing for group A streptococcal throat disease in primary care. *Scand J Infect Dis* 21:161-167.

Mäkelä, M. (1996) Do general practitioners need guidelines? *Scand J Prim Health Care* 14:2-3.

Mäkelä, M. & Leinonen, K. (1996) Diagnosis of maxillary sinusitis in Finnish primary care. Use of imaging techniques. *Scand J Prim Health Care* 14:29-35.

Mäkelä, M.J., Puhakka, T., Ruuskanen, O., Leinonen, M., Saikku, P., Kimpimaki, M., Blomqvist, S., Hyypia, T. & Arstila, P. (1998) Viruses and Bacteria in the Etiology of the Common Cold. *J. Clin. Microbiol.* 36:539-542.

Mangione-Smith, R., McGlynn, E.A., Elliott, M.N., Krogstad, P. & Brook, R.H. (1999) The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. *Pediatrics* 103:711-718.

Marchetti, F.M.D., Ronfani, L.M.D., Nibali, S.C.M.D., Tamburlini, G.M.D.P. & for the Italian Study Group on Acute Otitis, M. (2005) Delayed prescription may reduce the use of antibiotics for acute otitis media: A prospective observational study in primary care. *Arch Pediatr Adolesc Med* 159:679-684.

Margolis, D.J., Bowe, W.P., Hoffstad, O. & Berlin, J.A. (2005) Antibiotic treatment of acne may be associated with upper respiratory tract infections. *Arch Dermatol* 141:1132-1136.

Martikainen, J., Paakkari, P., Pajunen, R., Paldan, M. & Voipio, T. (2005) Finnish statistics on medicines 2004. National Agency for Medicines and Social Insurance Institution, Helsinki.

Maxwell, P.R., Rink, E., Kumar, D. & Mendall, M.A. (2002) Antibiotics increase functional abdominal symptoms. *Am J Gastroenterol* 97:104-108.

McCaig, L.F., Besser, R.E. & Hughes, J.M. (2002) Trends in antimicrobial prescribing rates for children and adolescents. *JAMA* 287:3096-3102.

McCormick, D.P., Chonmaitree, T., Pittman, C., Saeed, K., Friedman, N.R., Uchida, T. & Baldwin, C.D. (2005) Nonsevere acute otitis media: A clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 115:1455-1465.

McDermot, R.D.E. (1982) Social ramifications of control of microbial disease. *Johns Hopkins Med J* 151:302-312.

McIsaac, W.J., Kellner, J.D., Aufricht, P., Vanjaka, A. & Low, D.E. (2004) Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA* 291:1587-1595.

McManus, P., Hammond, M.L., Whicker, S.D., Primrose, J.G., Mant, A. & Fairall, S.R. (1997) Antibiotic use in the Australian community, 1990-1995. *Med J Aust* 167:124-127.

Melander, E., Björgell, A., Björgell, P., Ovhed, I. & Mölstad, S. (1999) Medical audit changes physicians' prescribing of antibiotics for respiratory tract infections. *Scand J Prim Health Care* 17:180-184.

Melander, E., Mölstad, S., Persson, K., Hansson, H.B., Söderström, M. & Ekdahl, K. (1998) Previous antibiotic consumption and other risk factors for carriage of penicillin-resistant Streptococcus pneumoniae in children. *Eur J Clin Microbiol Infect Dis* 17:834-838.

Melbye, H., Aaraas, I., Fleten, N., Kolstrup, N. & Mikalsen, J.I. (1995) Nytten av å teste C-reaktivt protein ved mulig nedre luftveisinfeksjon (The usefulness of a rapid C-reactive protein test in the managemwnt of adults with lower respiratory tract infection) (in Norwegian with English abstract). *Tidsskr Nor Laegeforen* 115:1610-1615.

Metlay, J.P. & Fine, M.J. (2003) Testing strategies in the initial management of patients with community-acquired pneumonia. *Ann Intern Med* 138:109-118.

Metlay, J.P., Kapoor, W.N. & Fine, M.J. (1997) Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 278:1440-1445.

Mills, G.D., Oehley, M.R. & Arrol, B. (2005) Effectiveness of beta-lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. *BMJ* 330:456-.

Ministry of Health and Social Security Iceland (2004).Statistics on drug use in Iceland 1994-2003. http://eng.heilbrigdisraduneyti.is/Information/nr/1777,

Mölstad, S., Eliasson, I., Hovelius, B., Kamme, C. & Schalen, C. (1988) Beta-lactamase production in the upper respiratory tract flora in relation to antibiotic consumption: a study in children attending day nurseries. *Scand J Infect Dis* 20:329-334.

Mölstad, S., Lundborg, C.S., Karlsson, A.K. & Cars, O. (2002) Antibiotic prescription rates vary markedly between 13 European countries. *Scand J Infect Dis* 34:366-371.

Monnet, D.L., Ferech, M., Frimodt-Möller, N. & Goossens, H. (2005) The more antibacterial trade names, the more consumption of antibacterials: A European study. *Clin Infect Dis* 41:114-117.

Monto, A.S. (1994) Studies of the community and family: acute respiratory illness and infection. *Epidemiol Rev* 16:351-373.

Monto, A.S. & Sullivan, K.M. (1993) Acute respiratory illness in the community. Frequency of illness and the agents involved. *Epidemiol Infect* 110:145-160.

Monto, A.S. & Ullman, B.M. (1974) Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 227:164-169.

Möttönen, M. & Uhari, M. (1992) Absences for sickness among children in day care. *Acta Paediatr* 81:929-932.

Munck, A.P., Gahrn-Hansen, B., Søgaard, P. & Søgaard, J. (1999) Long-lasting improvement in general practitioners' prescribing of antibiotics by means of medical audit. *Scand J Prim Health Care* 17:185-190.

Mäntyselkä, P., Miettola, J., Halinen, M., Lipponen, P., Hietakorpi, S. & Kumpusalo, E. (2003) Kuopion yhteispäivystystutkimus; Kuopion yhteispäivystyksen yleislääkäripäivystyksen käyntisyyt ja konsultaatiot (Causes of consultation to GPs in a regional on-call centre in Kuopio) (in Finnish). *Suomen Lääkärilehti* 58:415-418.

Nash, D.R., Harman, J., Wald, E.R. & Kelleher, K.J. (2002) Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. *Arch Pediatr Adolesc Med* 156:1114-1119.

NHS Centre for Reviews and Dissemination (1999) Getting evidence into practice. *Effective Health Care* 5:1-16.

Nicholson, K.G., Kent, J., Hammersley, V. & Cancio, E. (1997) Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 315:1060-1064.

Nissinen, A., Grönroos, P., Huovinen, P., Herva, E., Katila, M.L., Klaukka, T., Kontiainen, S., Liimatainen, O., Oinonen, S. & Mäkelä, P.H. (1995) Development of beta-lactamase-mediated resistance to penicillin in middle-ear isolates of Moraxella catarrhalis in Finnish children, 1978-1993. *Clin Infect Dis* 21:1193-1196.

Njalsson, T., Sigurdsson, J.A. & McAuley, R.G. (1996) Health problems in family practice. An Icelandic multicentre study. *Scand J Prim Health Care* 14:4-12.

Nordic Medico-Statistical Committee (Ed.) (2004) Medicines Consumption in the Nordic Countries 1999-2003. NOMESCO, Copenhagen.

NORM/NORM-VET 2004 (2005).Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. http://www.vetinst.no/inet_no/index.asp?strurl=1000586i, November 2005

Norrby, S.R., Nord, C.E. & Finch, R. (2005) Lack of development of new antimicrobial drugs: a potential serious threat to public health. *Lancet Infect Dis* 5:115-119.

Nuorti, J.P., Butler, J.C., Crutcher, J.M., Guevara, R., Welch, D., Holder, P. & Elliott, J.A. (1998) An outbreak of multidrug-resistant pneumococcal pneumonia and

114

bacteremia among unvaccinated nursing home residents. *N Engl J Med* 338:1861-1868.

Nurmi, T., Salminen, E. & Pönkä, A. (1991) Infections and other illnesses of children in day-care centers in Helsinki. II: The economic losses. *Infection* 19:331-335.

Nyman, K. & Raitasalo, R. (1978) Työstäpoissaolot ja niihin vaikuttavat tekijät Suomessa (Absence from work and factors behind it) (in Finnish) in: Kela (Ed) *Kansaneläkelaitoksen julkaisuja A* (Helsinki, Kansaneläkelaitos).

Nyquist, A.C., Gonzales, R., Steiner, J.F. & Sande, M.A. (1998) Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *JAMA* 279:875-877.

O'Connell, D.L., Henry, D. & Tomlins, R. (1999) Randomised controlled trial of effect of feedback on general practitioners' prescribing in Australia. *BMJ* 318:507-511.

Odenholt, I., Gustafsson, I., Lowdin, E. & Cars, O. (2003) Suboptimal antibiotic dosage as a risk factor for selection of penicillin-resistant Streptococcus pneumoniae: in vitro kinetic model. *Antimicrob Agents Chemother* 47:518-523.

Orr, P.H., Scherer, K., Macdonald, A. & Moffatt, M.E. (1993) Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. *J Fam Pract* 36:507-512.

Palmu, A., Puhakka, H., Rahko, T. & Takala, A.K. (1999) Diagnostic value of tympanometry in infants in clinical practice. *Int J Pediatr Otorhinolaryngol* 49:207-213.

Palmu, A., Syrjänen, R., Kilpi, T., Pursiainen, H., Puhakka, H., Rahko, T., Herva, E. & Takala, A. (2001) Negative pressure tympanograms in children less than 2 years of age--different bacterial findings in otitis media by tympanometric results. *Int J Pediatr Otorhinolaryngol* 61:61-69.

Palva, E., Alhava, E., Jalanka, H., Kujala, P., Lumio, J., Valtonen, V., Vuopio-Varkila, J. & Huovinen, P. (1994) MIKSTRA - mikrobilääkehoidon strategiat 1990-luvulla (MIKSTRA - antibiotic treatment strategies in the 1999s) (in Finnish). *Suomen Lääkärilehti* 49:1043-1044.

Peay, M.Y. & Peay, E.R. (1984) Differences among practitioners in patterns of preference for information sources in the adoption of new drugs. *Soc Sci Med* 18:1019-1025.

Peltola, H. (1996) Kliinikon mikrobilääkeopas (Clinical guidelines for antibiotic use) (in Finnish). Orion Oy,

Peltola, H. (2003a) Infektioiden globaalinen merkitys (Global implication of infections) (in Finnish), in: *Mikrobiologia ja infektiosairaudet*, Vol., pp. 217-224. Kustannus Oy Duodecim, Helsinki.

Peltola, H. (2003b) Infektiotaudit historian muokkaajina (Infectious diseases and history) (in Finnish), in: *Mikrobiologia ja infektiosairaudet*, Vol., pp. 14-25. Kustannus Oy Duodecim, Helsinki.

Perez-Cuevas, R., Guiscafre, H., Munoz, O., Reyes, H., Tome, P., Libreros, V. & Gutierrez, G. (1996) Improving physician prescribing patterns to treat rhinopharyngitis. Intervention strategies in two health systems of Mexico. *Soc Sci Med* 42:1185-1194.

Perz, J.F., Craig, A.S., Coffey, C.S., Jorgensen, D.M., Mitchel, E., Hall, S., Schaffner, W. & Griffin, M.R. (2002) Changes in antibiotic prescribing for children after a community-wide campaign. *JAMA* 287:3103-3109.

Pétursson, P. (2005) Why Non-Pharmacological Prescribing of Antibiotics? - A Phenomenological Investigation into the Rationale behind it from the GP's perspective. Master of Public Health Essay (Nordic School of Public Health).

Pichichero, M.E. (1999) Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics* 104:1384-1388.

Pihlajamäki, M., Kaijalainen, T., Huovinen, P. & Jalava, J. (2002) Rapid increase in macrolide resistance among penicillin non-susceptible pneumococci in Finland, 1996-2000. *J Antimicrob Chemother* 49:785-792.

Pihlajamäki, M., Kotilainen, P., Kaurila, T., Klaukka, T., Palva, E. & Huovinen, P. (2001) Macrolide-resistant Streptococcus pneumoniae and use of antimicrobial agents. *Clin Infect Dis* 33:483-488.

Pirhonen, I., Husman, T. & Pekkanen, J. (1994) Työikäisen väestön hengitystieinfektioiden yleisyys, lääkärissäkäynnit ja sairauspoissaolot (Frequency of and, medical attendance and sick leave in respiratory tract infections in a working-aged population) (in Finnish). *Suomen Lääkärilehti* 49:2538-2543.

Pitkäranta, A. & Hayden, F.G. (1998) Rhinoviruses: important respiratory pathogens. *Ann Med* 30:529-537.

Pönkä, A., Nurmi, T., Salminen, E. & Nykyri, E. (1991) Infections and other illnesses of children in day-care centers in Helsinki. I: Incidences and effects of home and day-care center variables. *Infection* 19:230-236.

Puhakka, H.J., Hagman, E., Heikkinen, T., Huovinen, P., Jero, J., Karma, P., Mäkelä, M., Ruuskanen, O. & Sairanen, S. (1999) Äkillisen poskiontelotulehduksen hoitosuositus (Acute otitis media: Finnish clinical practice guidelines) (in Finnish). *Duodecim* 115:2155-2161.

Puhakka, T., Heikkinen, T., Mäkelä, M.J., Alanen, A., Kallio, T., Korsoff, L., Suonpää, J. & Ruuskanen, O. (2000) Validity of ultrasonography in diagnosis of acute maxillary sinusitis. *Arch Otolaryngol Head Neck Surg* 126:1482-1486.

Puhakka, T., Mäkelä, M.J., Alanen, A. & et al. (1998) Sinusitis in the common cold. *J Allergy Clin Immunol* 102:403-408.

Pärnänen, H., Mäntyselkä, P., Kumpusalo, E. & Takala, J. (2001) Terveyskeskuslääkärissäkäyntien syyt Suomessa (Causes of GP consultations in Finland) (in Finnish). *Suomen Lääkärilehti* 56:3483-3487.

Ranki, A., Hyry, H., Jansson, T., Karvonen, J., Kontiainen, S., Kousa, M. & Mäkelä, M. (1999) Ihon primaarien bakteeri-infektioiden hoitosuositus (Bacterial skin-infections: Finnish clinical practice guidelines) (in Finnish). *Duodecim* 115:2139-2146.

Rautakorpi, U.-M., Honkanen, P., Huikko, S., Anttila, H., Klaukka, T., Leistevuo, J., Mäkelä, M., Palva, E., Roine, R., Sarkkinen, H., Varonen, H. & Huovinen, P. (2002) Hoitajat - liian vähän käytetty voimavara infektioiden hoidossa? (Nurses - too seldom used resource in treatment of infection patients?) (in Finnish). *Suomen Lääkärilehti* 57:4480-4483.

Reichler, M.R., Allphin, A.A., Breiman, R.F., Schreiber, J.R., Arnold, J.E., McDougal, L.K., Facklam, R.R., Boxerbaum, B., May, D., Walton, R.O. & et al. (1992) The spread of multiply resistant Streptococcus pneumoniae at a day care center in Ohio. *J Infect Dis* 166:1346-1353.

Reinikainen, L., Jaakkola, J.J.K. & Heinonen, O.P. (1988) Ilmankosteus toimistorakennuksen sisäilmatekijänä (Humidity as an indoor air factor in an office building) (in Finnish). *Suomen Lääkärilehti* 43:38-45.

Richards, D., Toop, L., Chambers, S. & Fletcher, L. (2005) Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial. *BMJ* 331:143-.

Rokstad, K., Straand, J. & Fugelli, P. (1995) Can drug treatment be improved by feedback on prescribing profiles combined with therapeutic recommendations? A prospective, controlled trial in general practice. *J Clin Epidemiol* 48:1061-1068.

116

Rosenfeld, R.M. (2002) Diagnostic certainty for acute otitis media. *Int J Pediatr Otorhinolaryngol* 64:89-95.

Rothermel, C.D. (2004) Penicillin and macrolide resistance in pneumococcal pneumonia: Does in vitro resistance affect clinical outcomes? *Clin Infect Dis* 38:346-349.

Rothman, R., Owens, T. & Simel, D.L. (2003) Does this child have acute otitis media? *JAMA* 290:1633-1640.

Rubin, M.A., Bateman, K., Alder, S., Donnelly, S., Stoddard, G.J. & Samore, M.H. (2005) A multifaceted intervention to improve antimicrobial prescribing for upper respiratory tract infections in a small rural community. *Clin Infect Dis* 40:546-553.

Rzeszutek, M., Wierzbowski, A., Hoban, D.J., Conly, J., Bishai, W. & Zhanel, G.G. (2004) A review of clinical failures associated with macrolide-resistant Streptococcus pneumoniae. *Int J Antimicrob Agents* 24:95-104.

Samore, M.H., Bateman, K., Alder, S.C., Hannah, E., Donnelly, S., Stoddard, G.J., Haddadin, B., Rubin, M.A., Williamson, J., Stults, B., Rupper, R. & Stevenson, K. (2005) Clinical Decision Support and Appropriateness of Antimicrobial Prescribing: A Randomized Trial. *JAMA* 294:2305-2314.

Sarkkinen, H., Hirvonen, T., Mäkelä, M. & Putto-Laurila, A. (1999) Nielutulehduksen hoitosuositus (Throat infection: Finnish clinical practice guidelines) (in Finnish). *Duodecim* 115:2162-2170.

Schwartz, R.H., Stool, S.E., Rodriguez, W.J. & Grundfast, K.M. (1981) Acute otitis media: toward a more precise definition. *Clin Pediatr (Phila)* 20:549-554.

Schwartz, R.K., Soumerai, S.B. & Avorn, J. (1989) Physician motivations for nonscientific drug prescribing. *Soc Sci Med* 28:577-582.

Seppä, Y., Bloigu, A., Honkanen, P.O., Miettinen, L. & Syrjala, H. (2001) Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch Intern Med* 161:2709-2713.

Seppälä, H., Klaukka, T., Lehtonen, R., Nenonen, E., Finnish Study Group for Antimicrobial Resistance & Huovinen, P. (1995) Outpatient use of erythromycin: link to increased erythromycin resistance in group A streptococci. *Clin Infect Dis* 21:1378-1385.

Seppälä, H., Klaukka, T., Vuopio-Varkila, J., Muotiala, A., Helenius, H., Lager, K. & Huovinen, P. (1997) The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med* 337:441-446.

Seppälä, H., Nissinen, A., Järvinen, H., Huovinen, S., Henriksson, T., Herva, E., Holm, S., Jahkola, M., Katila, M.-L., Klaukka, T., Kontiainen, S., Liimatainen, O., Oinonen, S., Passi-Metsomaa, L. & Huovinen, P. (1992) A-streptokokkien erytromysiiniresistenssi Suomessa (Erythromycin resistance in group A streptococci in Finland) (in Finnish). *Suomen lääkärilehti* 47:1317-1323.

Shefet, D., Robenshtok, E., Paul, M. & Leibovici, L. (2005) Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. *Arch Intern Med* 165:1992-2000.

Smith, H.S., Hughes, J.P., Hooton, T.M., Roberts, P., Scholes, D., Stergachis, A., Stapleton, A. & Stamm, W.E. (1997) Antecedent antimicrobial use increases the risk of uncomplicated cystitis in young women. *Clin Infect Dis* 25:63-68.

Smith, R.P. & Lipworth, B.J. (1995) C-reactive protein in simple community-acquired pneumonia. *Chest* 107:1028-1031.

Soares, S., Kristinsson, K.G., Musser, J.M. & Tomasz, A. (1993) Evidence for the introduction of a multiresistant clone of serotype 6B Streptococcus pneumoniae from Spain to Iceland in the late 1980s. *J Infect Dis* 168:158-163.

Sobel, J., D. & Kaye, D. (2005) Urinary Tract Infections, in: *Mandell, Douglas, Bennett's Principles and Practice of Infectious Diseases*, Vol., pp. 875-905. Elsevier, Philadelphia.

Socialstyrelsen (2001) Progress Report on Antimicrobial Resistance in: Socialstyrelsen (Ed) *The Microbial Threat* (Stockholm, Socialstyrelsen).

Steinke, D. & Davey, P. (2001) Association between antibiotic resistance and community prescribing: a critical review of bias and confounding in published studies. *Clin Infect Dis* 33(Suppl 3):S193-205.

Stewart, J., Pilla, J. & Dunn, L. (2000) Pilot study for appropriate anti-infective community therapy; Effect of a guideline-based strategy to optimize use of antibiotics. *Can Fam Physician* 46:851-859.

Stingemore, N., Francis, G.R., Toohey, M. & McGechie, D.B. (1989) The emergence of erythromycin resistance in Streptococcus pyogenes in Fremantle, Western Australia. *Med J Aust* 150:626-627, 630-621.

Stålsby Lundborg, C., Olsson, E., Mölstad, S. & Swedish Study Group on Antibiotic Use (2002) Antibiotic prescribing in outpatients: a 1-week diagnosis-prescribing study in 5 counties in Sweden. *Scand J Infect Dis* 34:442-448.

Syrjälä, H., Broas, M., Suramo, I., Ojala, A. & Lahde, S. (1998) High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clin Infect Dis* 27:358-363.

Söndergaard, J., Andersen, M., Stovring, H. & Kragstrup, J. (2003) Mailed prescriber feedback in addition to a clinical guideline has no impact: a randomised, controlled trial. *Scand J Prim Health Care* 21:47-51.

Takala, J., Rintanen, H., Linnakylä, M., Hartikainen, M. & Lyra, H. (1977a) Kunnanlääkärissäkäynnit sairausryhmittäin III; Päivystyskäyntien yleisimmät syyt Hankasalmen, Konneveden ja Rautalammin kunnissa (GP consultations by disease group III; Causes of on-call consultations in three municipalities) (in Finnish). *Suomen Lääkärilehti* 32:219-223.

Takala, J., Rintanen, H., Linnakylä, M., Hartikainen, M. & Lyyra, H. (1977b) Kunnanlääkärissä käynnit sairausryhmittäin II; Lääkärissäkäyntien yleisimmät syyt diagnoosiryhmittäin Hankasalmen, Konneveden ja Rautalammin kunnissa (GP consultations by disease group II; Causes of consultations by diagnosis in three municipalities) (in Finnish). *Suomen Lääkärilehti* 32:111-116.

Talbot, T.R., Poehling, K.A., Hartert, T.V., Arbogast, P.G., Halasa, N.B., Edwards, K.M., Schaffner, W., Craig, A.S. & Griffin, M.R. (2005) Seasonality of invasive pneumococcal disease: Temporal relation to documented influenza and respiratory syncytial viral circulation. *Am J Med* 118:285-291.

Teele, D.W., Klein, J.O. & Rosner, B. (1989) Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis* 160:83-94.

Thorsen, T. & Mäkelä, M. (Eds.) (1999) Changing Professional Practice; Theory and Practice of Clinical Guidelines Implementation. DSI Danish Institute for Health Services Research and Development, Copenhagen.

Tuomainen, L., Wallenius, K., Ahonen, R. & Palva, E. (1995) Väestön asenteita mikrobilääkehoitoon (The public's knowledge and perceptions of the antimicrobial drug treatment) (In Finnish with English symmary) in: Lääkelaitos (Ed) *Lääkelaitoksen julkaisusarja* (Helsinki, Lääkelaitos).

Unsworth, L. & Walley, T. (2001) Trends in primary care antibiotic prescribing in England 1994-1998. *Pharmacoepidemiol Drug Saf* 10:309-314.

Wallenius, S., Ahonen, R. & Enlund, H. (1997) Lääkemääräyskäytäntö ja siihen vaikuttaminen (How to influence on prescribing practices) (in Finnish) in:

118

Ministry of Social Affairs and Health (Ed) *Sosiaali- ja terveysministeriön monisteita* (Helsinki,

Valtonen, V. & Makkonen, T. (1981) Kapseli 10; Antimikrobinen lääkehoito (Antimicrobial treatment) (in Finnish). Lääkintöhallitus, Helsinki.

Van Balen, F.A., Aarts, A.M. & De Melker, R.A. (1999) Tympanometry by general practitioners: reliable? *Int J Pediatr Otorhinolaryngol* 48:117-123.

van der Meer, V., Neven, A.K., van den Broek, P.J. & Assendelft, W.J.J. (2005) Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 331:26-29.

Van Kuijk, K.C., Kuyvenhoven, M.M., AM, v.B.F., Rovers, M.M. & Verheij, T.J. (2006) International variation in guidelines on Acute Otitis Media: a comparison of 15 guidelines. *(submitted)*

Wang, E.E.L., Einarson, T.R., Kellner, J.D. & Conly, J.M. (1999) Antibiotic prescribing for canadian preschool children: evidence of overprescribing for viral respiratory infections. *Clin Infect Dis* 29:155-160.

Vanharanta, M., Voutilainen, S., Lakka, T.A., van der Lee, M., Adlercreutz, H. & Salonen, J.T. (1999) Risk of acute coronary events according to serum concentrations of enterolactone: a prospective population-based case-control study. *Lancet* 354:2112-2115.

Varonen, H., Mäkelä, M., Savolainen, S., Läärä, E. & Hilden, J. (2000) Comparison of ultrasound, radiography, and clinical examination in the diagnosis of acute maxillary sinusitis: a systematic review. *J Clin Epidemiol* 53:940-948.

Varonen, H. & Mäkelä, M.J. (1996) Suomalaiset hoitosuositukset (Finnish guidelines) (in Finnish). *Duodecim* 112:994-998.

Varonen, H., Savolainen, S., Kunnamo, I., Heikkinen, R. & Revonta, M. (2003) Acute rhinosinusitis in primary care: a comparison of symptoms, signs, ultrasound, and radiography. *Rhinology* 41:37-43.

Watson, R.L., Dowell, S.F., Jayaraman, M., Keyserling, H., Kolczak, M. & Schwartz, B. (1999) Antimicrobial use for pediatric upper respiratory infections: Reported practice, actual practice, and parent beliefs. *Pediatrics* 104:1251-1257.

Vehkasaari, M. (2002) Terveyskeskusten viroista hoitamatta 11,3 prosenttia (Eleven per cent of GP posts unattended) (in Finnish). *Suomen Lääkärilehti* 57:4858-4860.

Vehviläinen, A.T., Kumpusalo, E.A. & Takala, J.K. (1997) Reasons for referral from general practice in Finland. *Scand J Prim Health Care* 15:43-47.

Vehviläinen, A.T., Kumpusalo, E.A., Voutilainen, S.O. & Takala, J.K. (1996) Does the doctors' professional experience reduce referral rates? Evidence from the Finnish referral study. *Scand J Prim Health Care* 14:13-20.

Vehviläinen, A.T., Takala, J.K., Keinänen-Kiukaanniemi, S., Posti, S., Viinikainen, h. & Kumpusalo, E.A. (2005) Terveyskeskuksen päivystysajan lääkärissäkäynnit ja lähetteet erikoissairaanhoitoon (Consultations in and referrals from health centres at out-of-hours) (in Finnish). *Suomen Lääkärilehti* 60:1821-1825.

Velicer, C.M., Heckbert, S.R., Lampe, J.W., Potter, J.D., Robertson, C.A. & Taplin, S.H. (2004) Antibiotic use in relation to the risk of breast cancer. *JAMA* 291:827-835.

Welschen, I., Kuyvenhoven, M., Hoes, A. & Verheij, T. (2004a) Antibiotics for acute respiratory tract symptoms: patients' expectations, GPs' management and patient satisfaction. *Fam Pract* 21:234-237.

Welschen, I., Kuyvenhoven, M.M., Hoes, A.W. & Verheij, T.J.M. (2004b) Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. *BMJ* 329:431-433.

Verheij, T., Hermans, J., Kaptein, A. & Mulder, J. (1995) Acute bronchitis: course of symptoms and restrictions in patients' daily activities. *Scand J Prim Health Care* 13:8-12.

Westerholm, B., Grimsson, A., Kristensen, F., Soininen, R. & Öydvin, K. (Eds.) (1979) Nordic Statistics on Medicines 1975-1977. Nordic Council of Medicines, Helsinki.

Whitney, C.G., Farley, M.M., Hadler, J., Harrison, L.H., Lexau, C., Reingold, A., Lefkowitz, L., Cieslak, P.R., Cetron, M., Zell, E.R., Jorgensen, J.H. & Schuchat, A. (2000) Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. *N Engl J Med* 343:1917-1924.

WHO (2001).WHO Global Strategy for Containment of Antimicrobial Resistance. *Communicable Disease Surveillance & Response (CSR),* http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_DRS_2001_2_EN/en/, 24.11. 2005

WHO Collaborating Centre for drug Statistics Methodology (1996).ATC/DDD System. http://www.whocc.no/atcddd/, 29.11. 2005

WHO Model Prescribing Information (2001) Drugs used in bacterial infections. World Health Organization Geneva, Geneva.

WHO Scientific Working Group (1983) Antimicrobial resistance. *Bulletin of the World Health Organization* 61:383-394.

Williams Jr, J.W., Aguilar, C., Cornell, J., Chiquette E Dolor, R.J., Mäkelä, M., Holleman, D.R. & Simel, D.L. (2003).Antibiotics for acute maxillary sinusitis. *The Cochrane Database of Systematic Reviews,* http://www.thecochranelibrary.com, August 2005

Williams, J.W., Jr. & Simel, D.L. (1993) Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. *JAMA* 270:1242-1246.

Wipf, J.E., Lipsky, B.A., Hirschmann, J.V., Boyko, E.J., Takasugi, J., Peugeot, R.L. & Davis, C.L. (1999) Diagnosing pneumonia by physical examination: relevant or relic? *Arch Intern Med* 159:1082-1087.

Wise, R., Hart, T., Cars, O., Streulens, M., Helmuth, R., Huovinen, P. & Sprenger, M. (1998) Antimicrobial resistance; Is a major threat to public health. *BMJ* 317:609-610.

Witte, W., Cuny, C., Strommenger, B., Braulke, C. & Heuch, D. (2004) Emergence of new community accuired MRSA strain in Germany. *Eurosurveillance* 9:16-18.

Voipio, T. (Ed.) (2003) Lääkkeiden luokitus (ATC) ja määritellyt vuorokausiannokset (DDD) (Classification of drugs (ATC) and defined daily doses (DDD)) (in Finnish). National Agency for Medicines, Helsinki.

Yu, V.L., Chiou, C.C., Feldman, C., Ortqvist, A., Rello, J., Morris, A.J., Baddour, L.M., Luna, C.M., Snydman, D.R., Ip, M., Ko, W.C., Chedid, M.B., Andremont, A. & Klugman, K.P. (2003) An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clin Infect Dis* 37:230-237.

Ziegler, M.G., Lew, P. & Singer, B.C. (1995) The accuracy of drug information from pharmaceutical sales representatives. *JAMA* 273:1296-1298.

Zwar, N., Henderson, J., Britt, H., McGeechan, K. & Yeo, G. (2002) Influencing antibiotic prescribing by prescriber feedback and management guidelines: a 5-year follow-up. *Fam Pract* 19:12-17.

Zwar, N., Wolk, J., Gordon, J., Sanson-Fisher, R. & Kehoe, L. (1999) Influencing antibiotic prescribing in general practice: a trial of prescriber feedback and management guidelines. *Fam Pract* 16:495-500.

APPENDIXES

Tables

Table 1 ICD-10- and ICPC-classifications of most common infections in primary care

ICD-10-main class	Diagnosis	ICPC-main class
I Communicable diseases	scarlet fever	R
	bacterial and viral gastroenteritis	D
	erysipelas	S
	STDs* (female and male)	X, Y
	Herpes simplex and zoster, uncomplicated	S
	viral warts	S
	Mononucleosis	A
	viral conjunctivitis	F
	unspecified viral infection	A
	pityriasis versicolor, skin- and nail candidiosis and unspecified tinea	S
VII Diseases of the eye	blefaritis, chalzion, hordeolum, abscess of eyelid	F
	purulent conjunctivitis, dacryocystitis	F
	corneal infections and iritis	F
VIII Diseases of the ear	myringitis and acute otitis media	H
	earache, secretion from the ear	H
X Diseases of the respiratory tract	rhinitis and nasopharyngitis	R
	unspecified viral upper respiratory tract infection/common cold	R
	acute and chronic sinusitis	R
	tonsillitis, peritonsillar abscess	R
	laryngitis	R
	influenza	R
	viral or unspecified pneumonia	R
	bacterial pneumonia, aspiration pneumonia	R
	acute bronchitis and bronchiolitis	R
	chronic bronchitis, COPD**	R
	furunculosis of nose	R
XI Diseases of the gastrointestinal tract	perianal abscess	D
	stomatitis, gingivitis, periapical abscess	D
	cholecystitis, pancreatitis	D

Table 1 cont…

ICD-10-main class	Diagnosis	ICPC-main class
XII Diseases of skin	impetigo (primary and secondary)	S
	abscess, funruncel, cellulites pronychia	S
	lymfadenitis	B
	achne, chronic ulcer	S
XIII Diseases of the musculoskeletal organs	purulent arthritis	L
XIV Diseases of the genitourinary tract	urethritis, cystitis and pyelonephritis	U
	prostatitis	Y
	mastitis	X
	bartholinitis, vaginitis, salpingitis, PID***	X
XV Diseases of pregnancy, birth and weaning	mastitis during weaning	W
XVIII Other and symptoms	Cough, sore throat	R
	fever	A

ICD = International Classification of Diseases

ICPC = International Classification of Primary Care

*STD = Sexually Transmitted Disease

**COPD = Chronic Obstructive Pulmonary Disease

***PID = Pelvic Inflammatory Diasese

Table 2 Key characteristics used in selection of MIKSTRA study health centres

Health Centre	Population at end of 1997	No of GPs 1998	Type	Size	Hospital District	Prescriptions of antibiotics /1000inh. in 1996***
Asikkala	8 800	6	Rural	Small	Päijät-Häme	483
Espoo, Tapiola*	38 726	15	Urban	Large	Helsinki-Uusimaa	659
Haapavesi	8 283	6	Rural	Small	Pohjois-Pohjanmaa	541
Hamina+	26 697	15	R/U	Medium	Kymenlaakso	607
Helsinki, Alppiharju*	17 200	7	Urban	Large	Helsinki-Uusimaa	611
Helsinki, Latokartano*	12 111	6	Urban	Large	Helsinki-Uusimaa	611
Inari	7 716	6	Rural	Small	Lappi	395
Joutseno	11 423	6	Rural	Medium	Etelä-Karjala	510
Juva+	14 990	9	Rural	Medium	Etelä-/Itä-Savo	520
Jyväskylä	76 500	46	Urban	Large	Keski-Suomi	486
Kannus	6 300	4	Rural	Small	Keski-Pohjanmaa	660
Korpilahti+	12 751	8	R/U	Medium	Keski-Suomi	471
Kyrönmaa+	17 916	12	Rural	Medium	Vaasa	566
Lammi+	7 265	5	Rural	Small	Kanta-Häme	465
Masku+	13 281	7	Rural	Medium	Varsinais-Suomi	681
Mäntsälä	15 700	8	R/U	Medium	Helsinki-Uusimaa	716
Mänttä+	16 384	11	Rural	Medium	Pirkanmaa	502
Nilsiä	7 800	6	Rural	Small	Pohjois-Savo	571
Oulu	113 584	60	Urban	Large	Pohjois-Pohjanmaa	596
Pirkkala	11 848	8	R/U	Medium	Pirkanmaa	475
Rovaniemi city	34 600	23	R/U	Medium	Lappi	492
Rovaniemi	22 000	12	Rural	Medium	Lappi	498
Salo+	44 402	29	R/U	Medium	Varsinais-Suomi	542
Seinäjoki+	48 976	30	R/U	Medium	Etelä-Pohjanmaa	688
Suomussalmi	11 690	6	Rural	Medium	Kainuu	522

124

Table 2 cont…

Health Centre	Population at end of 1997	No of GPs 1998	Type	Size	Hospital District	Prescriptions of antibiotics /1000inh. in 1996***
Tormajärvi+	6 131	4	Rural	Small	Pohjois-Karjala	640
Turku	168 000	79	Urban	Large	Varsinais-Suomi	629
Ulvila+	14 513	8	R/U	Medium	Satakunta	629
Valkeakoski	20 700	14	R/U	Medium	Pirkanmaa	539
Varpaisjärvi	3 490	3	Rural	Small	Pohjois-Savo	(76) 530**
All	819 777	459				

*represent large cities, Espoo (201 000 inhabitants) and Helsinki (540 000 inhabitants)

+joint health centre of several municipalities

R/U: health centres formed by an urban city with surrounding small rural communities or of smaller municipalities contiguous to big cities

**not computerised pharmacy in 1996, figure from 1998 given for comparison

***Source: National prescription register

Table 3 Key characteristics used in the selection of control health centres

Health Centre	Population at end of year 2001	No of GPs 2002	Type	Size	Hospital District	Prescriptions of antibiotics/1000inh. in 1996***
Alahärmä	5 383	5	Rural	Small	Etelä-Pohjanmaa	638
Alavus+	17 454	16	Rural	Medium	Etelä-Pohjanmaa	579
Espoo, Viherlaakso*	58 500	27	Urban	Large	Helsinki-Uusimaa	660
Etelä-Pirkanmaa+	13 447	10	Rural	Medium	Pirkanmaa	
Forssa+	35 730	23	R/U	Medium	Kanta-Häme	622
Heinola	20 000	11	R/U	Medium	Päijät-Häme	483
Joensuu	52 140	31	Urban	Large	Pohjois-Karjala	547
Kaakkois-Savo+	9 190	7	Rural	Small	Etelä Savo	443
Kemi	24 936	10	Urban	Medium	Lappi	389
Keminmaa	8 900	7	Rural	Small	Lappi	481
Kiiminki	10 791	7	Rural	Small	Pohjois-Pohjanmaa	529
Kirkkonummi-Siuntio	35 500	24	R/U	Medium	Helsinki-Uusimaa	621
Lahti	94 706	55	Urban	Large	Päijät-Häme	498
Loimaan seutu+	18 882	14	Rural	Medium	Varsinais-Suomi	495
Luoteis-Satakunta+	14 576	11	Rural	Medium	Satakunta	528
Porvoo	43 050	33	R/U	Medium	Kymenlaakso	542
Raahe+	34 411	53	R/U	Medium	Pohjois-Pohjanmaa	633
Saarijärvi-Karstula+	21 630	11	Rural	Medium	Keski-Suomi	507
Salla	4 900	4	Rural	Small	Lappi	(48) 307**
Ylöjärvi	20 972	15	R/U	Medium	Pirkanmaa	(320) 506**
All	545 098	374				

*represents large city, Espoo (201 000 inhabitants)

+joint health centre of several municipalities

R/U: health centres formed by an urban city with surrounding small rural communities or of smaller municipalities contiguous to big cities

**not computerised pharmacy in 1996, figure from 1998 given for comparison

***Source: National prescription register

Questionnaires

TERVEYSKESKUSTEN PERUSTIETOLOMAKE 1998

Terveyskeskuksen nimi_____

Yhteyshenkilön nimi:_____
Osoite:_____

Puhelin:_____
Telefaksi:_____
E-mail: _____

Etäisyys lähimpään päivystävään sairaalaan (mikä?)
_____ _____ km
Etäisyys lähimpään keskussairaalaan (mikä?)
_____ _____ km
Terveyskeskuksen väestöpohja (mieluiten tarkka v:n 1997 lopun tieto):
_____as.
Väestöpohja kunnittain jos kuntainliitto/kuntayhtymä:

_____
_____

Vastaanottotoimipisteiden lkm: _____
Lääkäreiden lkm: _____

Onko seuraavassa lueteltujen infektioiden diagnostiikkaa hoitopäätöksineen
(myös lääkkeetön hoito ja pelkkä sairausloma) delegoitu hoitohenkilökunnalle?

Otiitti	kaikki lääkärille	osan hoitaa muu henkilökunta
Tonsilliitti	kaikki lääkärille	osan hoitaa muu henkilökunta
Sinuiitti	kaikki lääkärille	osan hoitaa muu henkilökunta
Bronkiitti	kaikki lääkärille	osan hoitaa muu henkilökunta
Iho-infektiot	kaikki lääkärille	osan hoitaa muu henkilökunta
Virtsatieinfektiot	kaikki lääkärille	osan hoitaa muu henkilökunta

Miten päivystys on järjestetty terveyskeskuksessanne?

Oma päivystys väestövastuulääkäreillä klo _____
Oma päivystys keskitetty, missä?/ klo _____
Päivystys muualla, missä?/ klo _____

Jos osa päivystyksestä tapahtuu muualla kuin omassa terveyskeskuksessanne, montako terveys-keskuksenne potilasta käyn vrk:ssa keskimäärin tässä 'ulkopuolisessa' päivystyksessä? _____

Mitä diagnostisia apuvälineitä Teillä on käytettävissänne infektiopotilaiden tutkimiseen päivystys tutkimuksina?

Laboratoriotutkimuksia/pikatestejä_____

_____

_____

Rtg-palveluita

_____

Sinus-UÄ   kyllä   ei
Tympanometri   kyllä   ei

Onko terveyskeskuksessanne Atk-pohjainen sairauskertomusjärjestelmä?:
                 ei   kyllä, mikä? _____

Saatteko laboratoriopalvelunne
             terveyskeskuksen omasta laboratoriosta?
             ostopalveluna muualta, mistä? _____

Minne terveyskeskuksessanne otetut mikrobiologiset näytteet normaalisti lähetetään tutkittaviksi (ts. mikä on laboratorionne tukilaboratorio)?
_____

Mitä röntgen- ym. kuvantamispalveluita terveyskeskuksessanne on saatavissa (omana tai ostopalveluna)?
_____
_____

Kuka tulkitsee röntgenkuvat?
Hoitava lääkäri noin _____% kuvista   Röntgenlääkäri noin _____ % kuvista

Kuka allekirjoittaa terveyskeskuksenne puolesta MIKSTRA-projektin kanssa tehtävän yhteistyösopimuksen?
_____

Palautus: projektipäällikkö Ulla-Maija Rautakorpi
STAKES/FinOHTA/MIKSTRA,
PL 220, 00531 Helsinki tai Telefaksi: 09 - 3967 2278

TERVEYSKESKUSTEN PERUSTIETOLOMAKE; seuranta 2002

Terveyskeskuksen nimi: _____

Terveyskeskuksen väestöpohja (mieluiten tarkka v. 2001 lopun tieto):
_____ as.
Väestöpohja kunnittain jos kuntainliitto/kuntayhtymä: _____
_____

Toimipisteiden lkm:

- lääkärin vastaanotot (työterveys ja opiskelijath mukaan lukien)_____
- terveysneuvonta (neuvolat, koulut) _____

Henkilökunnan vaihtuvuus ja virkojen täyttöaste tiedonkeruuviikolla 46 (11. -
17.11.2002):

	Lääkärit	Sairaanhoitajat	Terveydenhoitajat
Virkoja yhteensä viikolla 46			
Täytetty vakinaisesti viikolla 46			
Täytetty sijaisilla viikolla 46			
Osittain täyttämättä viikolla 46			
Kokonaan täyttämättä viikolla 46			
Montako viranhaltijaa on vaihtunut vv. 1998-2002 välillä (viikko 46 kunakin vuonna)?			
Montako uutta virkaa teillä on v.2002 vuoteen 1998 verrattuna?			

Onko terveyskeskuksessanne Atk-pohjainen sairauskertomusjärjestelmä?:
　　　　　□ ei 　　　□ kyllä, mikä? _____

Miten päivystys on järjestetty?

- Oma päivystys väestövastuulääkäreillä klo _____
- Oma päivystys keskitetty, missä? / klo _____
- Päivystys muualla, missä? / klo _____

Mitä päivystystutkimuksia teillä on käytettävissänne infektiopotilaiden
tutkimiseen?

- Sinus-UÄ 　　　□ kyllä 　　□ ei
- Tympanometri 　□ kyllä 　　□ ei
- Nieluviljely 　　□ kyllä 　　□ ei

- Virtsaviljely   □ kyllä   □ ei
- Nielu-pikatesti   □ kyllä   □ ei
- Virtsa-pikatesti   □ kyllä   □ ei
- CRP   □ kyllä   □ ei
- Muita laboratoriopalveluita? _____

    _____

- Rtg-palveluita? _____

    _____

- Kuka tulkitsee röntgenkuvat?
  Hoitava lääkäri noin _____% kuvista
  Röntgenlääkäri noin _____ % kuvista
- Minne terveyskeskuksessanne otetut mikrobiologiset näytteet lähetettään tutkittaviksi (ts. mikä on laboratorionne tukilaboratorio)?

    _____

Onko seuraavassa lueteltujen infektioiden diagnostiikkaa hoitopäätöksineen (myös lääkkeetön hoito ja pelkkä sairausloma) delegoitu hoitohenkilökunnalle?

- Otiitti   □ kaikki lääkärille   □ osan hoitaa muu henkilökunta
- Tonsilliitti   □ kaikki lääkärille   □ osan hoitaa muu henkilökunta
- Sinuiitti   □ kaikki lääkärille   □ osan hoitaa muu henkilökunta
- Bronkiitti   □ kaikki lääkärille   □ osan hoitaa muu henkilökunta
- Iho-infektiot   □ kaikki lääkärille   □ osan hoitaa muu henkilökunta
- Virtsatieinfektiot   □ kaikki lääkärille   □ osan hoitaa muu henkilökunta

Oletteko järjestäneet MIKSTRA-suosituksiin liittyvää koulutusta vielä vuoden 2002 aikana? Jos kyllä, mitä suosituksia olette käsitelleet ja milloin?

_____

_____

Vastaajan nimi:_____

Vastaajan e-mail:_____

Kiitos vastauksistanne!

Palauta lomake projektipäällikkö Ulla-Maija Rautakorvelle postitse:
Stakes/FinOHTA, PL220, 00531 Helsinki tai telefaxilla: (09) 3967 2278.

PERORAALISTEN MIKROBILÄÄKKEIDEN KÄYTTÖ PIRKANMAALLA

(täytetään jokaisesta infektiopotilaasta riippumatta siitä, määrätäänkö lääkehoitoa vai ei)

1. Potilaan syntymävuosi _____

2. Sukupuoli
- [1] nainen
- [2] mies

3. Onko kyseessä…
- [1] käynti päivystysvastaanotolla
- [2] käynti muulla vastaanotolla tai kotikäynti
- [3] puhelinkontakti

4. Päädiagnoosi
- [1] otiitti
- [2] tonsilliitti
- [3] sinuiitti
- [4] faryngiitti
- [5] tarkemmin määrittelemätön ylähengitystieinfektio
- [6] bronkiitti
- [7] pneumonia
- [8] iho-/haavainfektio
- [9] akne
- [10] ruusu (selluliitti)
- [11] suolistoinfektio (myös helikobakteeri)
- [12] virtsatieinfektio
- [13] gynekologinen infektio, sukupuolitauti tai mastiitti
- [14] muu infektio, mikä? _____
- [15] infektioprofylaksia
- [16] ei infektiotautia

5. Miten varmana pidät diagnoosia? Merkitse arviosi janalle

hyvin epävarma _____1_____2_____3_____4_____5_____ varma

6. Oireiden kesto
- [1] 0-3 vrk
- [2] 4-7 vrk
- [3] 8-14 vrk
- [4] 15 vrk tai pitempään

7. Määräsitkö potilaalle mikrobilääkettä?
- [1] kyllä
- [2] en
- [3] potilaalla oli mikrobilääkitys

8. Miten potilas suhtautui mahdolliseen mikrobilääkkeen määräämiseen?

vaati _____1_____2_____3_____4_____5_____ vastusti mikrobilääkitystä

MIKÄLI POTILAS EI NYT SAANUT MIKROBILÄÄKITYSTÄ, VOIT LOPETTAA LOMAKKEEN TÄYTTÄMISEN TÄHÄN.

9. Valittu mikrobilääkitys:

valmisteen nimi _____	vahvuus _____	annostus _____	pakkauskoko _____
valmisteen nimi _____	vahvuus _____	annostus _____	pakkauskoko _____
valmisteen nimi _____	vahvuus _____	annostus _____	pakkauskoko _____

10. Miten todennäköisenä pidät mikrobilääkkeen tehoa tässä tapauksessa?

epätodennäköisenä _____1_____2_____3_____4_____5_____ jokseenkin varmana

11. Oliko kyseessä…
- [1] uusi mikrobilääkehoitojakso?
- [2] aiemmin aloitetun mikrobilääkehoidon vaihto
- [3] aiemmin aloitetun mikrobilääkehoidon jatko?

Täyttäjän SV-tunnus tai leima _____

Terveyskeskuksen leima

PRESCRIBING OF ORAL ANTIBIOTICS IN PIRKANMAA REGION

(to be filled for all infection patients, including those who did not get antibiotic treatment)

1. Patient's year of birth _____

2. Sex

[1] female
[2] male

3. The visit is...

[1] an on duty visit (to outpatient clinic or home)
[2] a scheduled visit (to outpatient clinic or home)
[3] a telephone contact

4. Main diagnosis

[1] otitis
[2] tonsillitis
[3] sinusitis
[4] pharyngitis
[5] unspecified upper respiratory tract infection
[6] bronchitis
[7] pneumonia
[8] skin/wound infection

[9] acne
[10] erysipelas (deep cellulitis)
[11] gastrointestinal infection (incl. helicobacter)
[12] urinary tract infection
[13] gynaecological infection, STD or mastitis
[14] other infection, which? _____
[15] infection prophylaxis
[16] no infection

5. How reliable do you regard your diagnosis? Mark on the line.

very unreliable ———————————————— reliable
                1   2   3   4   5

6. Duration of symptoms

[1] 0-3 days
[2] 4-7 days
[3] 8-14 days
[4] 15 days or more

7. Did you prescribe an antibiotic to the patient?

[1] yes   [2] no   [3] the patient already had an antibiotic

8. What kind of expectations did the patient have on antibiotic prescribing?

demanded ———————————————— resisted antibiotic treatment
         1   2   3   4   5

IF YOU DID NOT PRESCRIBE AN ANTIBIOTIC TO THE PATIENT, PLEASE FINNISH HERE.

9. Prescribed antibiotic drug(s):

name of the preparation _____   strength _____   dosage _____   package size _____

name of the preparation _____   strength _____   dosage _____   package size _____

name of the preparation _____   strength _____   dosage _____   package size _____

10. How probable do you regard the curing effect of the antibiotic in this case?

improbable ———————————————— very probable
           1   2   3   4   5

11. Is this antibiotic treatment...

[1] the first one for this infection episode?
[2] a change to another antibiotic?
[3] a continuation to a previous treatment?

Doctor's identification _____

Name of the health centre

MIKSTRA – Infektioiden diagnostiikka ja hoito terveyskeskuksissa 1998

(täytetään jokaisesta infektiopotilaasta riippumatta siitä, määrätäänkö lääkehoitoa vai ei)

potilaan koodinumero ____

1. Potilaan syntymävuosi ____

2. Sukupuoli [1] nainen [2] mies

3. Onko kyseessä...
[1] päivystyskäynti (vastaanotolla tai kotikäynti)
[2] muu käynti (vastaanotolla tai kotikäynti)
[3] puhelinkontakti

4. Päädiagnoosi (vain yksi, hoitopäätösten kannalta keskeisin)
[1] otiitti
[2] tonsilliitti
[3] sinuiitti
[4] faryngiitti
[5] muu ylähengitystieinfektio
[6] akuutti bronkiitti
[7] infektion pahentama krooninen keuhkosairaus
[8] pneumonia
[9] konjunktiviitti
[10] iho-/haavainfektio (myös paise, akne ja tuore kontaminoitunut haava)
[11] ruusu, mastiitti tai muu syvä selluliitti
[12] virtsatieinfektio
[13] helikobakteeri-infektio
[14] suolistoinfektio
[15] sukupuolitauti
[16] gynekologinen infektio
[17] muu infektio, mikä? ____

5. Oireiden kesto potilaan tullessa vastaanotolle
[1] 0-3 vrk
[2] -7 vrk
[3] 8-14 vrk
[4] 15 vrk tai pitempään

6. Tehtiinkö potilaalle tämänhetkisen infektion vuoksi muita diagnostisia tutkimuksia kuin kliininen tutkimus?
[1] ei muita tutk.
[2] sinus-UÄ
[3] thorax-röntgen
[4] sinus-röntgen
[5] muu rtg-tutkimus, mikä?
[6] nielu-/virtsapikatesti
[7] nielu-/virtsaviljely
[8] viljely nenänielusta
[9] muu mikrobiol.tutk.
mikä?
[10] CRP
[11] leukosyytit
[12] muu verenkuva
[13] vasta-ainetutkimus
[14] muu tutkimus, mikä?

7. Teitkö potilaalle tämän sairauden vuoksi päivystyslähetteen tai konsultoitko potilaasta puhelimitse?
[1] ei kumpaakaan
[2] lähete sairaalan poliklinikalle
[3] lähete tk:n vuodeosastolle
[4] lähete erikoislääkärille
[5] konsultoin terveyskeskuslääkäriä
[6] konsultoin erikoislääkäriä

8. Tarvitsiko potilas sairauslomaa/huoltaja lapsenhoitolomaa tämän infektion vuoksi?
[1] ei [2] kyllä ____ pv (sisältäen myös mahdolliset omailmoituslomapäivät)

9. Määräsitkö potilaalle mikrobilääkettä per os tai i.m.?
[1] en [2] kyllä [3] potilaalla oli jo mikrobilääkitys

(Jos teet lopullisen päätöksen vasta myöhemmin, esim. laboratoriokokeitn valmistuttua, täytä lomake loppuun silloin)

10. Miten potilas suhtautui mahdolliseen mikrobilääkkeen määräämiseen?
(rengasta se numero, joka mielestäsi parhaiten vastaa mielikuvaasi potilaan odotuksista)

vaati	toivoi saavansa	suhtautui neutraalisti	oli epäilevä	vastusti
1	2	3	4	5

11. Valittu mikrobilääke (jos hoidon kesto poikkeaa pakkauskoon mukaisesta, anna myös kesto vrk:na):

valmisteen nimi	vahvuus	annostus	pakkauskoko	kesto vrk
valmisteen nimi	vahvuus	annostus	pakkauskoko	kesto vrk

12. Vaikuttiko mikrobilääkevalmisteen valintaan jokin seuraavista tekijöistä?
[1] allergia(epäily)
[2] aikaisempi haittavaikutus
[3] raskaus/imetys
[4] potilaan vaatimus/toivomus

13. Tähän infektioon määrätty tai suositeltu muu (oireenmukainen/paikallinen) lääkehoito?
(lääkereseptistä sekä pakkauskoko että kesto vrk:na, Muuten suositellusta vain hoidon kesto):

valmisteen nimi	vahvuus	pakkauskoko	hoidon kesto vrk
valmisteen nimi	vahvuus	pakkauskoko	hoidon kesto vrk

14. Oliko kyseessä...
[1] ensikäynti tämän infektioperiodin vuoksi?
[2] uusintakäynti ja moneskö kaikkiaan (ensikäynti mukaan lukien)? ____

15. Täyttäjä:
[1] Lääkäri, SV-tunnus tai leima [2] Th/sh, ____ nimikirjaimet
Sv-tunnus tai leima

MIKSTRA – Diagnosis and treatment of infections in primary care 1998

(to be filled in for all patients with infection, independent of therapy decisions)

patient code number _____

1. Year of birth _____

2. Gender   [1] female   [2] male

3. The consultation is…
- [1] an acute consultation (at an outpatient clinic or patient's home)
- [2] a scheduled consultation (at an outpatient clinic or patient's home)
- [3] a telephone contact

4. Main diagnosis (only the most important one)
- [1] otitis media
- [2] tonsillitis
- [3] sinusitis
- [4] pharyngitis
- [5] unspecified upper respiratory tract infection (URTI)
- [6] acute bronchitis
- [7] acute infection exacerbating a chronic pulmonary disease
- [8] pneumonia
- [9] conjunctivitis
- [10] skin/wound infection (incl. abscess, acne, and new contaminated wound)
- [11] erysipelas, mastitis or other deep cellulitis
- [12] urinary tract infection
- [13] helicobacter infection
- [14] gastrointestinal infection
- [15] sexually transmitted disease (STD)
- [16] gynaecological infection
- [17] other infection, which _____

5. Duration of the patient's symptoms at the time of consultation
- [1] 0 - 3 days
- [2] 4 - 7 days
- [3] 8 - 14 days
- [4] 15 days or more

6. Please tick all diagnostic tests which you prescribed for the patient
- [1] only clinical exam.
- [2] sinus ultrasound
- [3] thorax X-ray
- [4] sinus X-ray
- [5] other X-ray, which _____
- [6] throat/urine rapid test
- [7] throat/urine culture
- [8] nasopharyngeal culture
- [9] other microbiological sample, which? _____
- [10] CRP
- [11] leucocyte count
- [12] other haematological test
- [13] serological test
- [14] other exams, which? _____

7. Did you refer the patient to hospital or for a consultation?
- [1] neither
- [2] referred to hospital
- [3] admitted to health centre bed ward
- [4] referred to a specialist
- [5] consulted a GP
- [6] consulted a specialist

8. Did the patient need sick-leave / child care-leave because of the infection?
[1] no   [2] yes _____ days   (including self-reported sick-leave)

9. Did you prescribe an antibiotic to the patient?
(If you make the decision later, i.e. after the arrival of lab results, please complete this paper then)
[1] no   [2] yes   [3] the patient already had an antibiotic

10. What kind of expectations did the patient have on antibiotic prescribing?
(Please tick the number that in your opinion best illustrates the patient's expectations)

demanded	wished for	was neutral	was reluctant	resisted
1	2	3	4	5

11. Prescribed antibiotic drug(s)
(If duration of treatment differs from that counted from the package size, please indicate also the recommended duration in days)

name of the preparation	strength	dosage	package size	(duration, days)
name of the preparation	strength	dosage	package size	(duration, days)

12. Did any of the following factors influence the choice of the preparation?
- [1] (suspected) allergy
- [3] pregnancy/breast feeding
- [2] previous side-effect
- [4] patient's demand

13. Prescribed/recommended other (symptomatic) medication for this infection?
(If prescribed, give both package size and duration in days, if only recommended, give duration)

name of the preparation	strength	package size	duration, days
name of the preparation	strength	package size	duration, days

14. Was this consultation…
- [1] the first one for this episode of illness?
- [2] a later one, how many consultations all together? _____

15. This consultation was provided by
- [1] Doctor _____ identification number
- [2] Nurse _____ initials

MIKSTRA – Infektioiden diagnostiikka ja hoito terveyskeskuksissa 2002

potilaan koodinumero _____

(täytetään jokaisesta infektiopotilaasta riippumatta siitä, määrätäänkö lääkehoitoa vai ei)

1. Potilaan syntymävuosi _____

2. Sukupuoli
☐1 nainen ☐2 mies

3. Tupakoiko potilas tai lapsen vanhemmat kotona?
☐1 ei ☐2 kyllä noin _____ savuketta /vrk

4. Onko kyseessä…
☐1 päivystyskäynti (vastaanotolla tai kotikäynti)
☐2 muu käynti (vastaanotolla tai kotikäynti)
☐3 puhelinkontakti
☐4 sovittu kontrollikäynti

5. Päädiagnoosi (vain yksi, hoitopäätösten kannalta keskeisin)
☐1 otiitti (välikorvatulehdus)
☐2 tonsilliitti (nielurisatulehdus)
☐3 sinuiitti (sivuontelotulehdus)
☐4 faryngiitti (muu kurkkutulehdus)
☐5 tarkemmin määrittelemätön ylähengitystieinfektio (flunssa)
☐6 akuutti bronkiitti
☐7 infektion pahentama krooninen keuhkosairaus
☐8 keuhkokuume
☐9 konjunktiviitti (silmätulehdus)
☐10 iho-/haavainfektio (myös paise ja tuore kontaminoitunut haava)
☐10a akne
☐11 ruusu tai muu syvä selluliitti
☐11a mastiitti (rintatulehdus)
☐12 VTI: naisten **komplisoitumaton** kystiitti
☐12a virtsatieinfektio muu / **komplisoitu**
☐13 helikobakteeri-infektio
☐14 suolistoinfektio
☐15 sukupuolitauti
☐16 gynekologinen infektio
☐17 muu infektio, mikä? _____

6. Oireiden kesto potilaan tullessa vastaanotolle
☐1 0-3 vrk
☐2 4-7 vrk
☐3 8-14 vrk
☐4 15 vrk tai pitempään

7. Tehtiinkö potilaalle tämänhetkisen infektion vuoksi kliinisen tutkimuksen lisäksi muita diagnostisia tutkimuksia tai toimenpiteitä?
☐1 **ei muita tutk.**
☐2 sinus-UÄ
☐3 thorax-röntgen
☐4 sinus-röntgen
☐5 muu rtg-tutkimus, mikä? _____
☐6 nielu-/virtsa pikatesti
☐7 nielu-/virtsa viljely
☐8 viljely nenänielusta
☐9 muu mikrobiologinen tutkimus, mikä? _____
☐10 CRP
☐11 leukosyytit
☐12 muu verenkuva
☐13 vasta-ainetutkimus
☐14 muu tutkimus tai toimenpide, mikä? _____

8. Teitkö potilaalle tämän sairauden vuoksi päivystyslähetteen tai konsultoitko potilaasta puhelimitse?
☐1 **ei kumpaakaan**
☐2 lähete sairaalan poliklinikalle
☐3 lähete tk:n vuodeosastolle
☐4 lähete erikoislääkärille
☐5 konsultoin terveyskeskuslääkäriä
☐6 konsultoin muuta (erikois)lääkäriä

9. Tarvitsiko/saiko potilas sairauslomaa/huoltaja lapsenhoitolomaa tämän infektion vuoksi?
☐1 ei ☐2 kyllä _____ pv (sisältäen myös omailmoituslomapäivät)

10. Miten potilas suhtautui mahdollisen mikrobilääkkeen määräämiseen?
(rengasta se numero, joka mielestäsi parhaiten vastaa mielikuvaasi potilaan odotuksista)

halusi	toivoi saavansa	suhtautui neutraalisti	oli epäilevä	vastusti
1	2	3	4	5

11. Määräsitkö potilaalle mikrobilääkettä per os, i.m. tai i.v.? (paikallishoidot kohtaan 14.)
☐1 en ☐2 kyllä ☐3 potilaalla oli jo mikrobilääkitys ☐4 lääke määrättiin varalle

12. Valittu mikrobilääke (jos hoidon kesto poikkeaa pakkauskoon mukaisesta, anna myös kesto vrk:na):

valmisteen nimi _____ vahvuus _____ annostus _____ pakkauskoko _____ kesto vrk _____

valmisteen nimi _____ vahvuus _____ annostus _____ pakkauskoko _____ kesto vrk _____

13. Vaikuttiko mikrobilääkevalmisteen valintaan jokin seuraavista tekijöistä?
☐1 allergia(epäily)
☐2 aikaisempi haittavaikutus
☐3 raskaus/imetys
☐4 potilaan vaatimus/toivomus
☐5 toistuva/krooninen infektio
☐6 muu, mikä? _____

14. Tähän infektio-episodiin määrätty tai suositeltu oireenmukainen tai paikallinen lääkehoito?

valmisteen nimi _____ vahvuus _____ annostus _____ pakkauskoko _____ kesto vrk _____

valmisteen nimi _____ vahvuus _____ annostus _____ pakkauskoko _____ kesto vrk _____

15. Oliko kyseessä…
☐1 ensikäynti tämän infektioperiodin vuoksi?
☐2 uusintakäynti ja monesko kaikkiaan (ensikäynti mukaan lukien)? _____

16. Sovittiinko potilaalle uusintakäynti
☐1 ei
☐2 kyllä, _____ päivän kuluttua
☐3 kehotettiin tulemaan tarvittaessa
☐4 sovittiin soittoaika

17. Täyttäjä:
☐1 Lääkäri, SV-tunnus tai leima _____
☐2 Th/sh, nimikirjaimet _____
☐3 Tka, nimikirjaimet _____

18. Oletko osallistunut johonkin MIKSTRA-koulutukseen? ☐1 en ☐2 olen _____ kertaa

patient code number _____

MIKSTRA – Diagnosis and treatment of infections in primary care 2002

(to be filled in for all patients with infection, independent of therapy decisions)

1. Year of birth _____

2. Gender

[1] female [2] male

3. Does the patient (or a child's parents) smoke?

[1] no [2] yes _____ cigarettes /day

4. The consultation is…

[1] an acute consultation (at an outpatient clinic or patient's home)
[2] a scheduled consultation (at an outpatient clinic or patient's home)
[3] a telephone contact
[4] a scheduled follow-up visit

5. Main diagnosis (only the most important one)

[1] otitis media
[2] tonsillitis
[3] sinusitis
[4] pharyngitis
[5] unspecified upper respiratory tract infection (URTI / common cold))
[6] acute bronchitis
[7] acute infection exacerbating a chronic pulmonary disease
[8] pneumonia
[9] conjunctivitis
[10] skin/wound infection (incl. abscess and new contaminated wound)
[10a] acne
[11] erysipelas or other deep cellulitis
[11a] mastitis
[12] UTI: female uncomplicated cystitis
[12a] UTI: other / complicated
[13] helicobacter infection
[14] gastro-enteritis
[15] sexually transmitted disease (STD)
[16] gynaecological infection
[17] other infection, please specify _____

6. Duration of the patient's symptoms at the time of consultation

[1] 0-3 days
[2] 4-7 days
[3] 8-14 days
[4] 15 days or more

7. Please tick all diagnostic tests and interventions which you did or prescribed for the patient

[1] only clinical exam.
[2] sinus ultrasound
[3] thorax X-ray
[4] sinus X-ray
[5] other X-ray, which
[6] throat/urine rapid test
[7] throat/urine culture
[8] nasopharyngeal culture
[9] other microbiological sample, please specify
[10] CRP
[11] leucocyte count
[12] other haematological test
[13] serological test
[14] other tests, please specify

8. Did you refer the patient to hospital or for a consultation?

[1] neither
[2] referred to hospital
[3] admitted to health centre bed ward
[4] referred to a specialist
[5] consulted a GP
[6] consulted a specialist

9. Did the patient need sick-leave / child care-leave because of the infection?

[1] no [2] yes _____ days (including self-reported sick-leave)

10. What kind of expectations did the patient have on antibiotic prescribing?
(Please tick the number that in your opinion best illustrates the patient's expectations)

demanded	wished for	was neutral	was reluctant	resisted
1	2	3	4	5

11. Did you prescribe an antibiotic to the patient?

[1] no [2] yes [3] the patient already had an antibiotic [4] prescription 'in case'

12. Prescribed antibiotic drug(s) (If duration of treatment differs from that counted from the package size, please indicate also the recommended duration in days)

name of the preparation	strength	dosage	package size	(duration, days)
name of the preparation	strength	dosage	package size	(duration, days)

13. Did any of the following factors influence the choice of the preparation?

[1] (suspected) allergy
[2] previous side-effect
[3] pregnancy/breast feeding
[4] patient's request
[5] re-infection/chronic infection
[6] other, please specify _____

14. Prescribed/recommended other (symptomatic) medication for this infection

name of the preparation	strength	dosage	package size	(duration, days)
name of the preparation	strength	dosage	package size	(duration, days)

15. Was this consultation…

[1] the first one for this episode of illness?
[2] a re-consultation; how many consultations all together? _____

16. Was a follow-up visit recommended?

[1] no
[2] yes, in _____ days
[3] yes, if needed
[4] yes, a telephone contact

17. This consultation was provided by

[1] Doctor (identification number) _____
[3] Health assistant (initials) _____
[2] Nurse (initials) _____

18. Have you participated in MIKSTRA-training?

[1] no [2] yes _____ times

ORIGINAL PAPERS

The original papers have been reproduced with
the kind permission of the copyright holders.

Indication-based use of antimicrobials in Finnish primary health care

Description of a method for data collection and results of its application

Ulla-Maija Rautakorpi[1], Jukka Lumio[2], Pentti Huovinen[3] and Timo Klaukka[4]

[1]Pirkkala Health Centre, Pirkkala, [2]Department of Infectious Diseases, Internal Medicine, Tampere University Hospital, Tampere, [3]Antimicrobial Research Laboratory, National Public Health Institute, Turku, [4]The Social Insurance Institution, Helsinki, Finland.

Scand J Prim Health Care 1999;17:93–99. ISSN 0281-3432

Objective – To collect population-based information on treatment of infections with antibiotics in PHC.
Design – A questionnaire study for general practitioners (GPs).
Setting – All health centres of Pirkanmaa Hospital District in Finland.
Patients – Patients with any infection attending health centre during 1 week in November 1994.
Main outcome measures – An infection diagnosis by the GP.
Results – A total of 4150 questionnaires were received from 223 doctors. Respiratory tract infections comprised 80% of all infections. Of all patients 64% received antimicrobial treatment. Unspecified upper respiratory tract infections and pharyngitis were rarely treated with antimicrobials (10 and 21%, respectively), whereas patients with acute bronchitis received antibiotics as often (83%) as patients with otitis media (93%) or tonsillitis (86%). The most commonly prescribed substances were cephalosporins (19% of all antimicrobials), penicillin V (17%), and amoxycillin (17%). Half of the cephalosporin use could be regarded as overuse. Half of the sulphatrimethoprims were used for otitis media. A quarter of the patients expressed a desire to receive antibiotic treatment.
Conclusion – The method was practical, inexpensive, and successful in giving such information, which is needed for supervising the rational use of antibiotics in primary health care.

Key words: antibiotics, infection, treatment, primary health care.

Ulla-Maija Rautakorpi, MD, Pirkkala Health Centre, Töyssälänkuja 4 D, FIN-33960 Pirkkala, Finland.

In Finland, population 5.1 million, ∼5 milllion outpatient visits occur annually for infections, and 90% of all antibiotic treatment doses are prescribed in outpatient care (1).

Sales of systemic antibiotics in Finland have in recent years amounted to some FIM 600 million (USD 133 million) per year, which is about FIM 120 (USD 27) per inhabitant (1). Iceland and Finland have long shown the highest use of antibiotics in the Nordic countries (Fig. 1) (2). In Denmark and Norway the use of antibiotics is almost one third lower than in Finland and Iceland. There are probably no true differences in incidence of common infections in these countries, and the differences in antibiotic use rather derive from diverging practices and guidelines. Compared with the other Nordic countries, typical of Finnish antibiotic use are high use of cephalosporins and sulphatrimethoprim combinations and relatively low use of phenoxymethylpenicillin (2).

The increasing resistance of microbes to existing antimicrobial agents is a serious problem worldwide (3). Positive correlation between resistance and high use of antibiotics has been shown earlier in hospitals (4,5) and recently also in outpatient care (6,7). Especially worrying is the increasing resistance in many common community-acquired pathogens (8–12). Multiresistant strains are already a serious problem in many European countries, and signs of these strains are also appearing in the Nordic countries (10,13–15).

Antimicrobial agents that would exhibit totally new modes of action and be feasible for treating outpatient infections caused by resistant bacteria, are not expected to be developed in the near future (16,17). A need to rationalise outpatient antibiotic use has been discussed in Finland, but little has been done so far to actually implement any interventions. One reason for this has been the lack of sufficient, indication-based data on the use of antibiotics in primary care. In the present paper we describe a method to collect such information and present the results obtained.
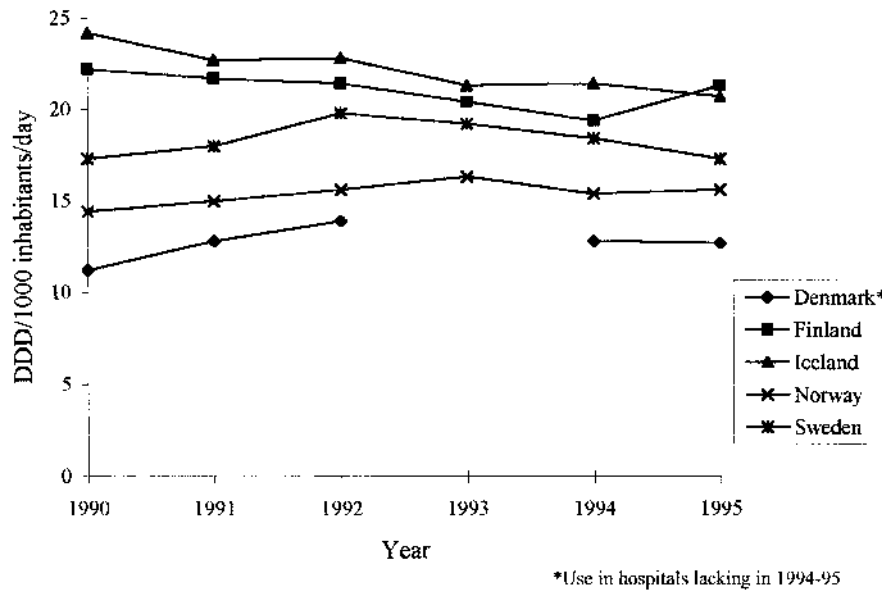
Fig. 1. Use of antibacterials (ATC-code J01) in the Nordic countries 1990–95.

MATERIAL AND METHOD

Pirkanmaa Hospital District in southern Finland has a population of 436000, which is 9% of the entire population of the country. The demography of the area is similar to the average in Finland. Primary health care services are provided by 35 municipalities at 20 health centres, which have 237 general practitioner (GP) posts in total. According to the Finnish Register of Prescriptions the crude pattern of antibiotic use in Pirkanmaa during 1994 approximated very closely to the mean pattern in Finland (Fig. 2).

Method

During 1 week Monday–Monday 08:00 in November 1994 all doctors at health centres in Pirkanmaa were asked to fill in a questionnaire for each patient with an infection, regardless of whether the patient received antibiotic treatment or not. The questions in the single page (A4 size) questionnaire are presented in Table I. Table II shows the classification of infections. In order not to interfere with customary prescription habits, diagnostic criteria were not standardised; instead, GPs used the criteria they were accustomed to in their daily work.

Self-estimations of reliability of the diagnosis, anticipated curative effect of the antibiotic, and patient expectations were indicated by making a tick on a visual analogue scale of 1–5, which had opposite statements at each end of the scale. For instance in the question regarding patient expectations, those demanded (scale number 1) occurred at one end of the scale and those resisted (scale number 5) at the other. For the other questions, answers were indi-

cated by ticking the respective boxes, except the medication, which was written. The questionnaire was pretested in actual prescribing situations. The completion of one questionnaire required on average 20 seconds when no antibiotic was prescribed, and 40 seconds when the patient received medicine.

Cases in which parenteral treatment was used (three cases of erysipelas and two of pneumonia) were included in the study. The diagnosis group "Other infection, which?" (n = 184) was checked, and when feasible reclassified, e.g. abscesses and infected
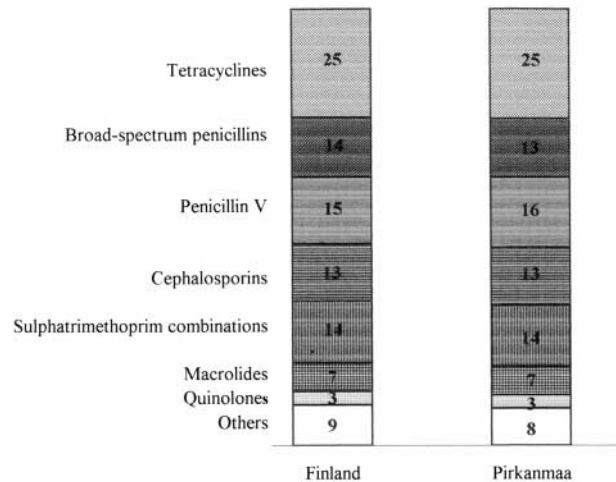

Fig. 2. Antibacterials for systemic use (J01): distribution (%) of use (DDD/1000 inhabitants/day) in the whole of Finland and in Pirkanmaa Hospital District in 1994.

Table I. Main contents of the questionnaire: The use of oral antimicrobial agents in Pirkanmaa

(To be completed for each patient with infection regardless of whether or not the patient receives antibiotics).

1.	Patient's year of birth
2.	Sex
3.	Type of visit (scheduled or home visit, on duty, telephone)
4.	Main diagnosis
5.	How reliable do you regard your diagnosis? (scale 1–5)
6.	Duration of patient's symptoms (four choices)
7.	Did you prescribe an antibiotic for the patient? (yes, no, the patient already had one)
8.	What was the opinion of the patient regarding possible prescription of an antibiotic? (scale 1–5)
9.[1]	The antibiotic(s) prescribed (name, dosage, package size)
10.[1]	How probable do you regard the curing effect of antibiotic in this case? (scale 1–5)
11.[1]	Was the treatment the first for this infection, a change to another treatment, or a continuation of a previous treatment?
12.	Doctor's professional identification code (stamp)
13.	Name of the health centre (stamp)

[1] Questions 9–11 to be answered only if the patient is given antibiotics.

wounds in this group were reclassified as "Skin/wound infections", and laryngitis and tracheitis as "Bronchitis".

RESULTS

A total of 4154 visits were recorded by 223 identified GPs. As the diagnosis was lacking in four cases, the final number of accepted questionnaires was 4150. Women comprised 57% of the patients, which is more than their proportion in the population of the district (52%). The percentage of patients aged 65 years or more was 8% (Table II) while they comprise 15% of the entire population. Children under 15 years of age comprised 39% of the patients with infection (19% of the population) and half of them were under 5 years of age.

Of the participating GPs, 95% completed < 40 questionnaires during the study week. As the estimated mean time needed to complete one questionnaire was 33 seconds, 95% of the GPs used 22 minutes per week at the most, i.e. an average of 4.4 minutes per working day to fill in the questionnaires.

The four most frequently appearing infections (unspecified upper respiratory tract infection, otitis media, bronchitis, and sinusitis) comprised together 62%, and all respiratory tract infections nearly 80% of all infections (Table II). Urinary tract infections, pneumonia, and skin infections were typical among elderly people. Children were overrepresented by comparison with their percentage in the population in most of the diagnosis groups.

Antibiotic treatment was prescribed to 64% of the patients with infection (Table II). Unspecified upper respiratory tract infections and pharyngitis (tonsillitis considered separately) were treated with antibiotics relatively rarely, while 83% or more of the patients received antibiotics for more specified respiratory tract infections. Nearly all the patients with otitis media, sinusitis, and urinary tract infection were treated with an antimicrobial agent. Antibiotic treatment was rare in gastrointestinal infections and in the mixed group of "Other infections", which included conjunctivitis (39%) and otitis externa (10%) as the largest groups.

Of the 223 participating GPs, 91 (41%) had written ten or more antibiotic prescriptions during the study week. These doctors had used an average of 6.4 different preparations, and ten of them 9 or more different preparations. The most frequently prescribed antimicrobial agents were cephalosporins (19%), phenoxymethylpenicillin and amoxycillin (17% each), and doxycycline (16%). Other major groups included macrolides (10%) and sulphatrimethoprim combinations (10%), while quinolones comprised only 1% of the prescriptions.

Three-quarters of the cephalosporins were first-generation preparations (cephalexin or cefadroxil) and the rest were second-generation (cefaclor or cefuroxime axetil). Cefaclor was mainly used for otitis media (77% of cefaclor prescriptions) and cefuroxime for sinusitis (45% of cefuroxime prescriptions). Doxycycline was practically the only tetracycline preparation used. The recently introduced macrolides, roxithromycin and azithromycin, comprised two-thirds of prescriptions in the macrolide group (43 and 26%, respectively). Diagnosis-based antibiotic choices are presented in Table III.

Half of the sulphatrimethoprim combinations were used to treat otitis media, which in practice means treating children (Table IV). Quinolones were very rarely used for respiratory infections. Cephalosporins were mostly used for skin infections and less frequently than other antibiotics for respiratory infections.

A quarter of the patients expressed a desire to obtain antibiotic treatment, while only 2% opposed the treatment. Positive expectations appeared most frequently in diseases with prominent and uncomfortable symptoms, such as gynaecological and urinary tract infections, sinusitis, and bronchitis (Table II). These expectations were related to patient's age (p < 0.001, SAS logistic regression analysis, F-test): 37% of elderly people but only 15% of children (or their parents) wanted antimicrobial treatment. Male and

Table II. Characteristics of visits, by infection diagnosis, in primary health care during 1 week in November 1994 in Pirkanmaa Hospital District, Finland.

Diagnosis	No. of cases	Distribution	Treated with antibiotics	Children (0–14 years)[1]	Patients >65 years[2]	Patient desired antibiotic (1–2/5)[3]	Curing effect probable (4–5/5)[3]	Diagnosis reliable (4–5/5)[3]
	n	%	%	%	%	%	%	%
Unspecified URTI[4]	884	21	10	49	4	13	66	82
Otitis media	675	16	93	84	1	21	93	97
Bronchitis	566	14	83	26	13	38	84	88
Sinusitis	446	11	93	14	7	34	89	91
Tonsillitis	371	9	86	38	2	27	95	91
Pharyngitis	230	6	21	25	4	13	47	85
Pneumonia	82	2	85	33	23	29	92	87
Respiratory tract infections, all	3254	78	63	44	6	24	89	89
Skin infections	295	7	83	17	15	28	95	95
Urinary tract infections	234	6	95	7	37	43	92	92
Gastrointestinal infections	96	2	18	28	10	11	88	89
Gynaecological infections (incl. STDs and mastitis)	84	2	76	2	7	38	98	88
Other infections	187	4	25	44	7	27	70	86
All infections	4150	100	64	39	8	26	89	89

[1] The percentage of children 0–14 years of age among the inhabitants was 19%.
[2] The percentage of people aged 65 years or over among the inhabitants was 15%.
[3] The prescribing doctor's own perception given on a scale of 1–5.
[4] URTI, upper respiratory tract infection.

female patients did not differ in this respect. Prolonged symptoms increased patient requests significantly ($p < 0.01$), especially in bronchitis, pharyngitis, and unspecified upper respiratory tract infactions. On the other hand, pressure from patients to obtain antibiotic treatment was on average lowest in infections for which less medication was given, e.g. gastrointestinal infections, pharyngitis, and unspecified upper respiratory tract infections.

DISCUSSION

Our data collection method was practical and successful at giving in-depth information on the treatment of various infections with antimicrobials in primary health care. The method is also suitable for collecting diagnosis-based information for evaluation of compliance with national recommendations. The direct costs of the present study were only some FIM 35 000 (USD 7800).

No official source was available to assess the coverage of the study. However, a participation rate of 223/237 identified GPs is very high and indicates good motivation. In a questionnaire study one month after the present study (data not presented), 92% of the doctors estimated that they had filled in a questionnaire for more than 80% of their patients with infection during the study week.

The present study provides explanations for the relatively high level of use of antimicrobial agents in Finland. One of these is that all major groups of infections, except unspecified upper respiratory tract infection and pharyngitis, were mostly treated with antibiotics.

Treating almost all cases of acute otitis media with antibiotics is consistent with current recommendations in Finland. Unspecified upper respiratory tract infections, pharyngitis, and acute bronchitis are mainly regarded as viral diseases with no antibiotic benefit (18–22). Although the first two diseases mentioned were relatively seldom treated with antibacterials (in 10 and 21% of cases, respectively), this practice was not applied to acute bronchitis, which was often (83%) treated with antibiotics. One explanation for this may be that the bronchitis patients wanted to obtain antibiotic treatment more often than patients with unspecified upper respiratory tract infections or pharyngitis. However, patients cannot be solely to

Table III. Antibiotics chosen (%) for various infections in primary health care during 1 week in Pirkanmaa, Finland.

	Otitis media (n = 590) %	Bronchitis (n = 443) %	Sinusitis (n = 400) %	Unspecified URTI[1] and pharyngitis (n = 148) %	Tonsillitis (n = 306) %	Pneumonia (n = 64) %	Skin infections (n = 220) %
Penicillin V	11	5	5	23	77	8	12
Amoxycillin	39	15	28	8	2	3	2
Cephalosporins	20	8	14	10	19	14	69
Doxycycline	1	39	37	33	0.3	14	2
Macrolides	2	25	7.5	21	1.3	56	4
Sulphatrimethoprim	24	6	8	4	0	0	5
Other	3	2	0.5	1	0.4	5	6
All antibiotics	100	100	100	100	100	100	100

[1] URTI, upper respiratory tract infection.

blame because the GPs concerned estimated in most cases (84%) that antibiotic treatment would benefit the patient. Thus, both doctors and patients appeared in general to believe that acute bronchitis demands antimicrobial treatment, in spite of the opposite official recommendations. In the marketing of antimicrobials, acute bronchitis is mentioned as an equal indication among such infections as otitis media, sinusitis, and pneumonia. This may give the GPs a wrong impression of the status of antimicrobials in the treatment of bronchitis. However, this biased attitude is not only a Finnish phenomenon (20). More attention should obviously be devoted to clarifying the diagnostic and treatment criteria of this disease and educating both doctors and the general population.

Managing sore throat with antibiotics is mainly focused on treating group A *Streptococci*. When a smear culture or antigen test, taken from a sore throat, is positive for *Streptococci*, the disease is more probably called tonsillitis than pharyngitis, thus, leaving viral infections more to the latter group. This probably explains the large difference in the percentage of patients treated with antimicrobials in these diagnoses.

The low level of use of erythromycin in our study, 31% of the macrolide group (n = 61), is in line with the recommendation given to Finnish doctors in 1991 to diminish its use, due to increased resistance of *Streptococci* group A to erythromycin (9,23). The correlation between high level of use of erythromycin and resistance was later verified (6). Sales statistics have shown decreased use of macrolides since the recommendation was issued. Our present study confirms that GPs in this case have complied with current recommendations, and that macrolides are only

rarely used to treat infections that are usually caused by group A *Streptococci*. If similar future recommendations are given, the method developed here would be suitable for monitoring their effects in practice.

The use of cephalosporins has increased four-fold in Finland from 1987 to 1992, while its use in Denmark, Norway, and Iceland has been much lower and fairly stable (2). First-generation cephalosporins are recommended in Finland as the drug of choice for skin infections, and in the case of penicillin allergy, for tonsillitis. According to our present results, these diagnoses explain 42% of the use. However, the 47% of cephalosporins that are used for respiratory tract infections other than tonsillitis can be regarded as overrepresentation and even counter to recommendations. First-generation cephalosporins seldom result in increased microbiological benefit over the more recommended drugs in sinusitis, bronchitis, or pharyngitis. The popularity of cephalosporins in otitis media may be based on the pleasant taste of the mixtures and on active marketing. The second-generation cephalosporins can also be microbiologically justified in some cases of otitis, but probably not as widely as they were used here. Furthermore, although cefuroxime axetil represented only 7% (38/516) of all cephalosporins in the present study, it accounted for 85% (17/20) of all reported severe cases of cephalosporin-induced colitis in Finland during 1990–1995 (24). Using such medicine to treat common and mild or self-limiting respiratory infections cannot be justified when safer alternatives are available.

Sulphatrimethoprim combination is regarded as dangerous in Denmark and Sweden (25); its use has also been decreasing in Norway, while in Iceland it has been used at least as widely as in Finland (2). The

Table IV. The percentage of various infections (%) as indications for use of different antibiotics in primary health care in Pirkanmaa, Finland.

Diagnosis	Penicillin V (n = 462) %	Amoxycillin (n = 500) %	Cephalosporins (n = 516) %	Doxycycline (n = 425) %	Macrolides (n = 255) %	Sulphatrimethoprim (n = 283) %	Quinolones (n = 36) %
Otitis media	14	50	23	2	4	50	0
Tonsillitis	51	1	12	1	2	0	0
Sinusitis	5	22	11	35	11	11	3
Unspecified URTI[1] and pharyngitis	8	3	4	12	12	3	0
Bronchitis	5	14	7	41	44	10	0
Pneumonia	1	1	2	2	14	0	3
Respiratory tract infections, all	84	91	59	93	87	74	6
Skin infections	6	1	30	1	4	4	6
Gastrointestinal infection	0	1	1	0	0	0	14
Urinary tract infection	0	1	2	0	0	17	60
Gynaecological infection (incl. STDs and mastitis)	1	1	2	1	0	0	14
Other infections	9	5	6	5	9	5	0
All infections	100	100	100	100	100	100	100

[1] URTI, upper respiratory tract infection.

fairly high level of use of sulphatrimethoprim in treating otitis media in Finland is not contradictory to the Finnish recommendations, and it mainly explains its high consumption in general. Sulphatrimethoprim mixtures have a relatively pleasant taste for children and they are inexpensive and often microbiologically justified. Severe side effects of sulphatrimethoprim have not been reported among children in Finland. However, this antimicrobial is not recommended as the drug of choice in otitis media, but rather as a good second choice. Observations made in Iceland on the colonisation of multiresistant strains of pneumococci in children after recurrent treatment with antibacterials, especially sulphatrimethoprim combinations (7), may result in re-evaluation of the status of this pharmaceutical, as well as antibacterials in general, in treating paediatric infections.

In conclusion, our simple data collection method gave the detailed information on the treatment of infections with antimicrobials in primary health care, that is necessary for supervising the rational use of antibiotics. The method is also useful for quality assurance and for monitoring changes in prescription practices. With minor modifications the questionnaire can be used to obtain information on other aspects of treating infections, and a similar model could be applied in studying the prescribing of other groups of drugs as well.

REFERENCES
1. Finnish Statistics on Medicines 1994. Helsinki: National Agency for Medicines and The Social Insurance Institution, 1995.
2. Nordic Statistics on Medicines 1993–1995. Uppsala: Nordic Council on Medicines, 1996.
3. Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–73.
4. Søgaard P. The epidemiology of antibiotic resistance in three species of the Enterobacteriaceae and the relation to consumption of antimicrobial agents in Odense University Hospital. Dan Med Bull 1989;36:65–84.
5. Gerding DN, Larson TA, Hughes RA, Weiler M, Shanholtzer C, Peterson LR. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. Antimicrob Agents Chemother 1991;35:1284–90.
6. Seppälä H, Klaukka T, Lehtonen R, Nenonen E, The Finnish Study Group for Antimicrobial Resistance, Huovinen P. Outpatient use of erythromycin: link to increased erythromycin resistance in group A *Streptococci*. Clin Infect Dis 1995;21:1378–85.

7. Arason VA, Kristinsson KG, Sigurdsson JA, Stefánsdóttir G, Mölstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. BMJ 1996;313:387–91.

8. Stingemore N, Francis GRJ, Toohey M, McGechie DB. The emergence of erythromycin resistance in *Streptococcus pyogenes* in Fremantle, Western Australia. Med J Aust 1989;150:626–27, 630–1.

9. Seppälä H, Nissinen A, Järvinen H, Huovinen S, Henriksson T, Herva E, et al. Resistance to erythromycin in group A *Streptococci*. N Engl J Med 1992;326:292–7.

10. Baquero F, Martinez-Beltran J, Loza E. A review of antibiotic resistance patterns of *Streptococcus pneumoniae* in Europe. J Antimicrob Chemother 1991;28 (Suppl C):31–8.

11. Reichler MR, Allphin AA, Breiman RF, Schreiber JR, Arnold JE, McDougal LK, et al. The spread of multiply resistant *Streptococcus pneumoniae* at a day care center in Ohio. J Infect Dis 1992;166:1346–53.

12. Rosdahl VT, Westh H, Jensen K. Antibiotic susceptibility and phage type pattern of Staphylococcus aureus strains isolated from patients in general practice compared to strains from hospitalized patients. Scand J Infect Dis 1990;22:315–20.

13. Kristinsson KG, Hjalmarsdottir MA, Steingrimsson O. Increasing penicillin resistance in pneumococci in Iceland. Lancet 1992;339:1606–7.

14. Soares S, Kristinsson KG, Musser JM, Tomasz A. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. J Infect Dis 1993;168:158–63.

15. Kalin M. Antibiotikaresistens hos pneumokocker. Hotfull utveckling i allt fler länder (Antibiotic resistance in pneumococci. A threatening development in more and more countries). Läkartidningen 1994;91:2219–22.

16. Gibbons A. Exploring new strategies to fight drug-resistant microbes. Science 1992;257:1036–8.

17. Travis J. Reviving the antibiotic miracle. Science 1994;264:360–2.

18. Orr P, Scherer K, McDonald A, Moffat M. Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. J Fam Pract 1993;36:507–12.

19. Jørgensen AF, Coolidge J, Pedersen PA, Petersen KP, Waldorff S, Widding E. Amoxicillin in treatment of acute uncomplicated exacerbations of chronic bronchitis. Scand J Prim Health Care 1992;10:7–11.

20. Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis? Commentary. Lancet 1995;345:665.

21. Zwar NA, Gordon JJ, Sanson-Fisher RW. Antibiotic and benzodiazepine prescribing by general practice trainees. Med J Aust 1994;161:491–3.

22. Melbye H. Klarer vi å redusere bruken av antibiotika ved akutt bronkitt? (Are we managing to reduce the use of antibiotics in acute bronchitis?). Tidsskr Nor Lægeforen 1995;115:1930–1.

23. Huovinen P, Klaukka T. Erytromysiinin käyttöä vähennettävä (The use of eryhtromycin must be reduced). Suom Lääkäril 1991;46:3241.

24. Lumio J. Montako antibioottia terveyskeskuslääkäri tarvitsee? (How many antibiotics do a health centre GP need?). Suom Lääkäril 1996;51:3133–5.

25. Friis H. Sulfa med trimetoprim – en farlig kombination (Sulpha and trimethoprim – a dangerous combination). Ugeskr Læger 1987;149:2563–5.

ORIGINAL ARTICLE

Antibiotic Use by Indication: A Basis for Active Antibiotic Policy in the Community

ULLA-MAIJA RAUTAKORPI[1], TIMO KLAUKKA[2], PEKKA HONKANEN[3], MARJUKKA MÄKELÄ[4], TUULI NIKKARINEN[5], ERKKI PALVA[6], RISTO ROINE[4], HANNU SARKKINEN[7] and PENTTI HUOVINEN[8] on behalf of the MIKSTRA Collaborative Study Group*

From the [1]Pirkkala Health Centre, Pirkkala, [2]Social Insurance Institution, Helsinki, [3]Kemi Health Centre, Kemi, [4]Finnish Office for Health Care Technology Assessment, Research and Development Centre for Welfare and Health, Helsinki, [5]Finnish Medical Society Duodecim, Helsinki, [6]National Agency for Medicines, Helsinki, [7]Päijät-Häme Central Hospital, Lahti and [8]Antimicrobial Research Laboratory, National Public Health Institute, Turku, Finland

The aim of this study was to survey current treatment practices for common infections in primary care as a basis for implementation of recently released evidence-based guidelines for community-acquired infections. A point-prevalence survey was conducted in 30 health centres in the Finnish primary care system with a population base of 819,777. All patients consulting the health centres for an infection during a 1-week period were included in the study. The main outcome measures were the prevalence of antibiotic prescription and the selection of drugs by infection diagnosis. Of the 7777 recorded consultations, 85% were with a physician and the rest with a nurse. The most common cause for a visit was respiratory tract infections (74%), followed by skin/wound infections and urinary tract infections (both 6%). The infection panorama varied markedly according to age: in the youngest children (< 5 y) 84% of the infections were respiratory tract infections whereas the corresponding figure for patients > 65 y was 50%; the proportions of visits for urinary tract infections in these age groups were 7% and 26%, respectively. Of the patients with acute bronchitis, 70% were treated with antimicrobial agents, mostly macrolides (39%) and doxycycline (36%). Of the otitis media patients, 53% were treated with amoxicillin, 16% with macrolides and 16% with sulphatrimethoprim. Macrolides were mostly used to treat otitis media (31%), acute bronchitis (26%) and sinusitis (20%). In conclusion, antimicrobial agents are still used excessively in Finland, particularly for the treatment of acute bronchitis. Moreover, the selection of drugs for treating sinusitis and otitis media is non-optimal; macrolides and cephalosporins are frequently chosen unnecessarily. Knowledge of the indication-based prescription practices for antimicrobial agents is essential in order to improve the treatment habits of primary care physicians. The data obtained in this study provide a unique tool for the active and targeted implementation of evidence-based guidelines for primary care physicians.

P. Huovinen, Antimicrobial Research Laboratory, National Public Health Institute, PO Box 57, FI-20521 Turku, Finland

INTRODUCTION

Increasing bacterial resistance to antimicrobial agents is a major health threat throughout the world (1, 2). This alarming increase has emerged over the last decade and although the problem has been evident for many years, little has been done to tackle it (3). In hospitals, antibiotic policies, in conjunction with sound hospital hygiene, comprise an important part of best practice. In the community setting, although important (4), hygiene measures are difficult to apply and are probably not as effective as in hospitals. New, more potent antimicrobial agents may be discovered in the future but antibiotic policies, in particular those which are less resistance-selective, are needed as well (5, 6).

In Finland, which has a population of 5 million, 2.5 million courses of antimicrobials are prescribed annually in the primary healthcare system and 80% of these courses are used for the treatment of respiratory tract infections. In 1998, the cost of antimicrobial medication in the primary

healthcare system was $\approx$ 60 million Euros, most of which was borne by the patients.

At the end of the last decade a decrease in the use of antimicrobial agents in the primary healthcare system in Finland was evident (7, 8). However, the use of antimicrobial agents in Finland is still noticeably higher than that in the other Nordic countries. Only Iceland has the same high level of use as Finland. A favourable decreasing trend in antibiotic usage has been especially evident in Sweden (9), whereas in two other Nordic countries, Norway (10) and Denmark (11), the use of antimicrobial agents has shown only a slight decrease. A partial explanation for the fairly high level of use in Finland could be the customary prescription of antibiotic courses of long duration (12).

MIKSTRA is a joint research and development programme designed to optimize diagnostic and treatment practices for common infections in the Finnish primary healthcare system whilst maintaining optimal cost-effectiveness and patient safety (13, 14). Particular attention is paid to the evaluation of indication-based diagnostic and treatment practices for infections in the primary healthcare system. Infection-specific evidence-based guidelines were

---

* The members of the MIKSTRA Collaborative Study Group are listed at the end of the paper.

drawn up by the Finnish Medical Society Duodecim as part of its Current Care (Käypä hoito) programme (15), which is supported by the Finnish Ministry of Social Affairs and Health and by hospital districts. New national guidelines for 6 common acute infections in primary care (otitis media, throat infection, acute sinusitis, acute bronchitis, skin infections and urinary tract infections) were published in 1999–2000 in a medical journal and on the Internet (16). Bacterial resistance is monitored by the FiRe (Finnish Study Group for Antimicrobial Resistance) programme (17).

To improve the antibiotic treatment practices in the primary healthcare system in Finland, a 5-y randomized trial of implementing evidence-based guidelines for common infectious diseases was started as part of the MIKSTRA programme. The aim of the main trial is to evaluate the effect of introducing the 6 new guidelines on diagnostic and treatment practices in primary care. The health centres participating in the MIKSTRA programme implement 3 of the 6 guidelines during the first study period and the remaining 3 during the second period. Implementation is done using problem-based learning (18) in half of the health centres and academic detailing (19) with feedback in the other half. This study reports baseline data on the infection panorama and indication-based antimicrobial treatment practices in the Finnish primary healthcare system before the new guidelines were introduced.

MATERIALS AND METHODS

Local authorities are responsible for the organization of Finnish healthcare services, and therefore primary healthcare services are based at local health centres (20, 21). In March 1998, we sent a letter to all Finnish health centres ($n = 258$) to inquire whether they would be interested in participating in a trial with the objective of

changing the management of common infectious diseases towards a more evidence-based direction. Of the 82 health centres that expressed their willingness to participate, 30 were enrolled in the study. These were selected to be representative of the whole country with respect to type (rural/urban), size and geographical location (14). In addition, the number of antibiotic prescriptions per 1000 inhabitants in 1997 was 1 criterion used for enrolment. In the 30 MIKSTRA health centres the average number of antibiotic prescriptions per year was 552 (range 393–703) per 1000 inhabitants, which compares favourably with the national average (543) and range (291–794). The population covered by the chosen health centres is 819,777 people (16% of the Finnish population) and there are ≈450 health centre physicians among the personnel surveyed.

During 1 calendar week in November 1998, physicians and nurses were asked to collect data using a structured case report form about every patient consulting for an infectious disease. The data collected included patient age and gender, the main diagnosis, use of diagnostic tools, prescription of antimicrobials and other medications and number of consultations during this infectious episode. The data collection method and questionnaire were piloted previously (22) and the questionnaire is available in English on our website (14). The case report forms were collected at the health centres and mailed to the MIKSTRA office. The data were processed using Excel and SAS software.

RESULTS

The data collected comprised a total of 7777 consultations at the health centres during the study week. The number of consultations at the different health centres varied from 39 to 1235 (2–25/1000 inhabitants). Eighty-five percent of patients saw a physician. Almost two-thirds (60%) of all patients were female. Children < 15 y comprised 38% of the patients, and over half of these were < 5 y, while 7% of the patients were > 65 y. Of the entire population of Finland, children account for 20% and the elderly for 15%.

Most visits were first consultations, but 19% of patients

Table I. *Infection diagnoses of primary healthcare patients during a 1-week period in 30 MIKSTRA health centres*

Diagnosis	n	(%)	Percentage of children (0–14 y)	Percentage of symptom duration 0–3 d before the visit	Percentage of first visits with the infection	Percentage of patients who received antimicrobials
URTI	1926	(25)	43	52	88	9
Otitis media	1229	(16)	82	58	76	88
Throat infection	942	(12)	30	60	85	44
Sinusitis	927	(12)	13	13	74	83
Acute bronchitis	555	(7)	32	17	79	71
Chronic lung disease exacerbated by infection	103	(1)	16	17	78	62
Pneumonia	75	(1)	31	24	55	69
All respiratory tract infections	5757	(74)				
Skin/wound infections	480	(6)	21	45	78	68
Urinary tract infections	436	(6)	7	73	84	80
Conjunctivitis	334	(4)	52	78	90	1
Intestinal infections	276	(3)	36	76	91	1
Gynaecological and sexually transmitted infections	131	(2)	1	29	84	47
Other infections	363	(5)	31	51	77	18
All infections	7777	(100)	38	48	81	48

Table II. *Infection frequency (%) in different age groups (n = 7777)*

Diagnosis	Age group			
	<5 y (*n* = 1629)	5–14 y (*n* = 1348)	15–64 y (*n* = 4255)	≥ 65 y (*n* = 537)
URTI	30	26	24	11
Otitis media	40	26	5	4
Throat infection	5	15	15	4
Sinusitis	1	8	17	13
Acute bronchitis	6	6	8	11
Chronic lung disease exacerbated by infection	0	1	1	5
Pneumonia	1	1	1	2
All respiratory tract infections	84	81	71	50
Skin/wound infections	2	5	7	13
Urinary tract infections	1	1	6	26
Conjunctivitis	7	5	3	4
Intestinal infections	2	4	4	2
Gynaecological and sexually transmitted infections	0	0	3	1
Other infections	4	4	5	4
All infections	100	100	100	100

had consulted the centre previously at least once for the same infection. Return visits were, on average, more common among those who had attended a health centre for pneumonia, sinusitis or otitis media (Table I). Of all infection patients studied, 2.1% were referred for secondary care, including those referred to hospital (1.5%).

Three-quarters (74%) of the patients attended a health centre for a respiratory tract infection (Table I). The most common diagnoses were unspecified upper respiratory tract infections (URTI; 25%) and otitis media (16%), followed by throat infections and sinusitis (both 12%). Variations in the infection panorama between different age groups of patients were evident, as respiratory tract infections comprised 83% of all infections in children < 5 y but only 50% in the oldest age group of patients aged ≥ 65 y (Table II). In the youngest age group, URTI and otitis media comprised 70% of all infections, with incidence rates of 52% in the older children (5–14 y), < 30% in adults and < 20% in elderly patients. The oldest age group was the only one in which respiratory tract infections was not among the 2 most common diagnoses; urinary tract infections was the main diagnosis in this patient group, followed by skin infections and sinusitis. The proportion of children was small among patients with sinusitis and urinary tract or gynaecological infections (Table I).
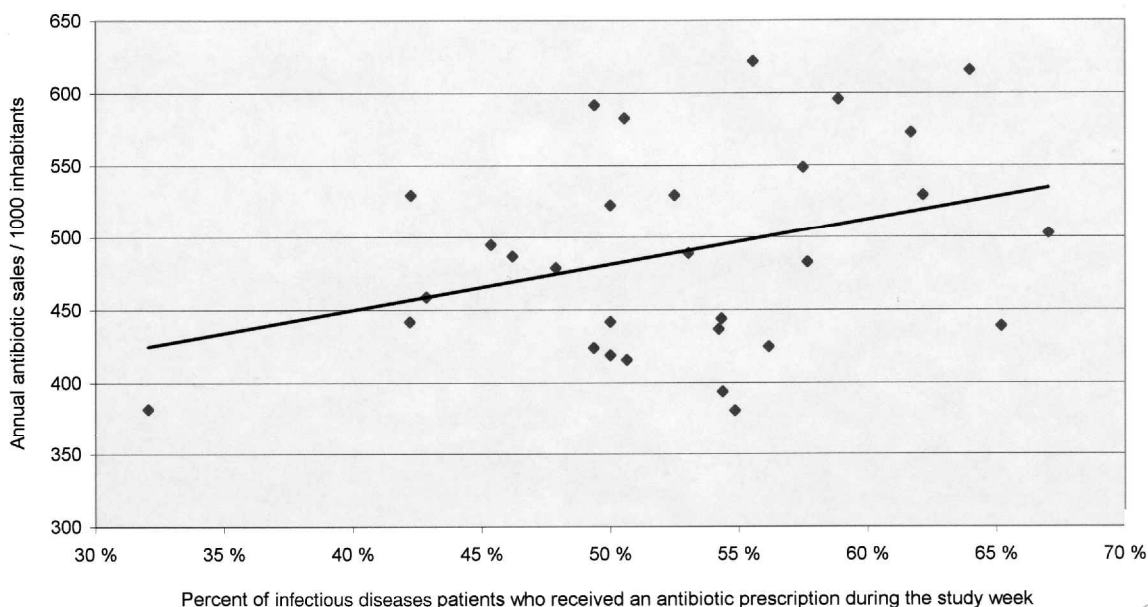

Fig. 1. Prescribing rate (for visits to doctors only) and annual antibiotic sales in 30 study health centres.

Table III. *Antimicrobial agents (%) used in different therapeutic indications*

	Amoxicillin (n = 995)	Penicillin V (n = 447)	Macrolides (n = 582)	Cephalosporins (n = 582)	Doxycycline (n = 480)	Sulphatrimethoprim (n = 227)	Quinolones (n = 70)
URTI	5	5	8	3	7	2	–
Otitis media	58	14	31	14	2	62	1
Throat infection	2	65	3	13	2	<1	–
Sinusitis	27	7	20	12	51	13	4
Acute bronchitis	7	3	26	2	29	3	–
Chronic lung disease exacerbated by infection	<1	<1	4	1	4	1	–
Pneumonia	<1	1	5	1	1	<1	–
All respiratory tract infections	99	95	97	46	96	81	5
Skin/wound infections	<1	3	1	46	1	3	6
Urinary tract infections	<1	–	–	3	–	15	79
Intestinal infections	–	–	–	–	–	–	–
Gynaecological and sexually transmitted infections	<1	–	2	<1	2	–	1
Other infections	<1	2	<1	5	1	1	9
All infections	100	100	100	100	100	100	100

Of all patients, 48% had experienced symptoms for ≤ 3 d before seeking medical attention (Table I). Seeking medical attention quickly was a feature of patients with conjunctivitis and intestinal and urinary tract infections. More than half of the patients with otitis media and throat infections also sought medical attention within 3 d of symptom onset, while less than 1 in 5 of those with sinusitis or bronchitis presented this quickly.

Oral antimicrobial treatment was prescribed for 48% of the patients (Table I) and this percentage was roughly the same for both adults and children. Medication was most commonly prescribed for patients who had attended for otitis media (88%) and sinusitis (83%). The prescription rate was also quite high among those who suffered from urinary tract infections (80%) and acute bronchitis (71%). The prescription of oral antimicrobial agents was least common for intestinal infections (1%) and for URTI (9%) and obviously for conjunctivitis, which is usually treated with topical preparations.

The prescription rate varied considerably between the different health centres. In 4 health centres > 60% of the patients and in 5 health centres < 40% received an antibiotic prescription. The highest prescription rate was 65% and the lowest 28%. To reveal the annual prescription activity in different health centres and to compare this with the prescription rate during the study week, the number of prescriptions per 1000 inhabitants according to the statistics of the National Insurance Institution is also presented (Fig. 1). The annual prescription activity and the prescription rate observed in this study are correlated but not statistically significantly (*p* = 0.061).

The distribution of antimicrobials used in adults and children varied markedly due to different infections. Doxycycline was the most commonly prescribed antimicrobial agent for adults (20% of all antimicrobial prescriptions), while amoxicillin was most popular in children (45%).

There is a variation in the medication profile of different infections (Fig. 2). The most frequently used drugs were
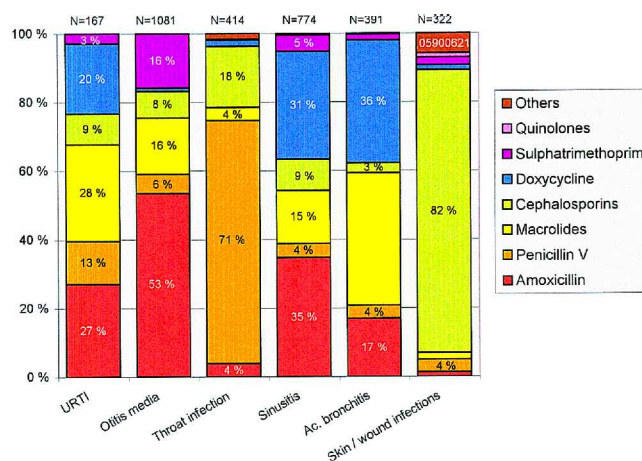

Fig. 2. Antimicrobial prescriptions for various infections.

macrolides and amoxicillin. In otitis media, amoxicillin, sulphatrimethoprim and macrolides were the most frequently used drugs. For throat infection, penicillin V and cephalosporins were the most frequently used drugs. For patients with sinusitis, amoxicillin and doxycycline and for acute bronchitis, macrolides and doxycycline were the most frequently prescribed antimicrobial agents. Skin and wound infections were mainly treated with cephalosporins.

One in 3 urinary tract infections (32%) were treated with plain trimethoprim. Mecillinam (18%), nitrofurantoin (16%) or fluoroquinolones (16%), were chosen only half as frequently compared with trimethoprim.

Antimicrobial policies can also be analysed by looking at the distributions of diagnoses within each drug group (Table III). Over half of the prescriptions for amoxicillin were used for the treatment of otitis media. The most frequent indication for penicillin V was throat infection, which accounted for 65% of the prescriptions. Macrolides were used mainly for three infections: otitis media, bronchitis and sinusitis. Almost half (46%) of all prescriptions for cephalosporins were for skin infections, and the same proportion of prescriptions was used to treat all respiratory tract infections taken together. Doxycycline was the first-line drug for sinusitis, accounting for approximately half of the prescriptions. The most frequent therapeutic indication for sulphatrimethoprim compounds was otitis media.

DISCUSSION

This study shows that 48% of patients with an infectious disease received oral antimicrobial treatment in Finland. The highest prescription rate, 88%, was for patients with otitis media. In addition, 83% of patients with sinusitis and 71% with acute bronchitis received antimicrobial treatment. However, only 44% of patients with a throat infection received antimicrobial treatment, which is well in line with the prevalence of streptococcal infections. The fact that only 9% of patients with unspecified respiratory tract symptoms—most of viral origin—received antimicrobial treatment was a favourable finding.

The data in the present study were collected in 1998, before the publication of the evidence-based Current Care guidelines in 1999 and 2000. Infection-based analysis of drug choices shows a need for the new guidelines. As expected, there is a big variation in the spectrum of different antimicrobial agents used in different indications. A major problem was the use of antimicrobial agents for acute bronchitis: 71% of patients received an antimicrobial prescription. Although acute bronchitis is mostly a self-limiting disease (23), this issue is known to be difficult for both patients and doctors (24). In contrast, the antibiotic choices in throat infections were quite satisfying: 89% of patients were treated with penicillin V or first-generation cephalosporins active against beta-haemolytic Streptococci. In addition, skin and wound infections, mostly caused by

Staphylococcus aureus and Streptococcus pyogenes, were treated in 82% of cases with first-generation cephalosporins. However, surprisingly, 40% of patients with otitis media were treated with macrolides and sulphatrimethoprim, although amoxicillin or penicillin V have traditionally been the drugs of choice in Finland. In addition, the proportion of macrolides and cephalosporins used in the treatment of respiratory tract infections appeared to be somewhat excessive. However, as second- and third-generation cephalosporins are not recommended for use as first- or second-line drugs for any of the most common community-acquired infections, the fact that 92% of the cephalosporins belonged to the first generation, i.e. cefalexin and cefadroxil, was a positive finding.

There are several factors that influence prescribing. The first, and most important, is the diagnosis. The diagnostic procedure of general practitioners varies widely. Although some drug recommendations have always been based on diagnosis, their effect is probably only indirect, as in primary care the diagnosis and the decision to medicate are intricately linked. The physician seems to decide first whether to prescribe an antimicrobial at all and then to adjust the diagnosis to fit the decision (25). This was also seen in a study in Iceland, where physicians were reminded to decrease the use of unnecessary antibiotic treatments because of the increased rate of resistant pneumococci (26). After this recommendation, the number of unspecified respiratory tract infection diagnoses increased while the number of otitis media diagnoses decreased. This change in diagnostic procedure gave physicians an opportunity to avoid prescribing antibiotics. Whatever the case, the antimicrobial prescription—as all our guidelines—should be based on diagnosis, which determines not only the antimicrobial drug used but also whether an antimicrobial drug is prescribed at all.

Active data collection itself may also have a temporary influence on the prescription habits of the physicians. This is a fact that cannot be avoided. There are also seasonal variations in infection epidemiology but although the epidemiology of infections varies, it is most likely that the treatment habits for different infections do not change remarkably. We collected the data during the second full week in November. This time was chosen to avoid a change in the infection panorama caused by an influenza epidemic, which usually starts in Finland in December or January. Although the correlation between annual antimicrobial sales and prescribing rate in our study is not statistically significant we believe that our sample is representative of the health centres, considering the influence of confounders such as epidemics outside the data collection week on the national annual statistics.

Treatment guidelines vary in quality (27) and even evidence-based recommendations vary in different countries according to national policies and the type of healthcare organization. Different opinions on antibiotic use can easily

be supported by relevant publications. Although it has been estimated that 20–50% of the antimicrobial prescriptions used in primary healthcare are unnecessary (1), it is difficult to give precise and commonly acceptable guidelines in order to improve antibiotic prescription habits. However, with knowledge of the actual indication-based use of antimicrobials it is possible to identify which changes are most essential and how they should be targeted.

Data on indication-based usage provide us with the tools to extend and focus the discussion of the most reasonable antibiotic policies in Finland. When the evidence-based guidelines for common infections were released, these data helped us to target the MIKSTRA education programme to the most prominent deviations from guideline recommendations, as recommended for the most effective change (28). As far as we know, our data are unique and according to our knowledge there are no other studies that take into account the whole infection panorama with which to compare our results.

In conclusion, the purpose of the MIKSTRA programme is to act as a stepwise, cyclical means of changing clinical practice. The effects of the newly released evidence-based guidelines on prescription habits will be followed over a 3-y year period from 2000 to 2002. Feedback will be given to the groups responsible for the guidelines as well as to the primary care physicians. We are convinced that supervision of indication-based prescription habits is an essential tool in delivering targeted information to physicians and in changing the non-optimal antimicrobial prescription practices.

ACKNOWLEDGEMENTS

CONTRIBUTORS

All the authors are members of the MIKSTRA Steering Committee and were involved in the design of the study and also in the interpretation of the results and in writing the paper. All the authors also contributed to the final version of the study. The members of the MIKSTRA Collaborative Study Group organized and collected the basic data for the study.

The members of the MIKSTRA Collaborative Study Group are as follows: Irja Laaksonen, Asikkala Health Centre; Markku Kanerva, Tapiola Health Centre, Espoo; Anne Niemelä, Haapavesi Health Centre; Timo Virtanen, Hamina Health Centre; Liisa Toppila, Alppiharju Health Centre, Helsinki; Camilla Mårtenson, Latokartano Health Centre, Helsinki; Kari Penttilä, Inari Health Centre; Marjatta Kaitila, Joutseno Health Centre; Jarmo Lappalainen, Juva-Puumala-Sulkava Health Centre; Jarmo J. Koski, Jy-

väskylä City Health Centre; Anu Kurikkala, Kannus Health Centre; Timo Kankaanpää, Muurame Health Centre, Korpilahti; Matti Norja, Kyrönmaa Health Centre; Antti Salmio, Lammi-Tuulos Health Centre, Lammi; Sirkka-Liisa Hiltunen, Masku Health Centre; Esko Nukari, Mäntsälä Health Centre; Kauko Koivisto, Mänttä Health Centre; Esa Asikainen, Nilsiä Health Centre; Olli Sipilä, Oulu Health Centre; Jouko Hietala, Pirkkala Health Centre; Antti Piiroinen, Rovaniemi City Health Centre; Pasi Tonteri, Rovaniemi Health Centre; Seppo Junnila, Salo Health Centre; Markku Valli, Seinäjoki Health Centre; Marja-Liisa Laitinen, Suomussalmi Health Centre; Maarit Karppinen, Tohmajärvi Health Centre; Eero Vaissi, Turku Health Centre; Kyösti Lemmetty, Ulvila Health Centre; Marketta Klemola, Valkeakoski Health Centre; and Risto Kettunen, Varpaisjärvi Health Centre.

REFERENCES

1. Wise R, Hart T, Cars O, Struelens M, Helmuth R, Huovinen P, et al. Antimicrobial resistance is a major threat to public health. Br Med J 1998; 317: 609–10.
2. Standing Medical Advisory Committee, Subgroup on Antimicrobial Resistance. The path of least resistance. London: Department of Health, 1998.
3. Huovinen P, Cars O. Control of antimicrobial resistance: time for action. Br Med J 1998; 317: 613–4.
4. Uhari M, Möttönen M. An open randomised controlled trial of infection prevention in child day-care centers. Pediatr Infect Dis J 1999; 18: 672–7.
5. Seppälä H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effects of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. N Engl J Med 1997; 337: 441–6.
6. Finnish Study Group for Antimicrobial Resistance, Huovinen P, Seppälä H, Kataja J, Klaukka T. The relationship between erythromycin consumption and resistance in Finland. Ciba Found Symp 1997; 207: 36–46.
7. Rautakorpi UM, Lumio J, Huovinen P, Klaukka T. Finnish antibiotic prescribing in change? Nordic Conference of General Practitioners, Reykjavik, June 1997 [abstract].
8. Klaukka T, Huovinen P, Palva E. Use of antibiotics decreases in outpatient care. Suom Lääkäril 1999; 54: 2143–6 (in Finnish).
9. Mölstad S, Cars O. Major change in the use of antibiotics following a national programme: Swedish Strategic Programme for rational use of antimicrobial agents and surveillance of resistance (STRAMA). Scand J Infect Dis 1999; 31: 191–9.
10. Øydvin K (ed.). Drug consumption in Norway 1994–1998. Oslo: Norsk Medisinaldepot AS, 1999 (in Norwegian).
11. Landberger JH. Antibiotic use rises again. Forbrug-Priser-Tilskud, No. 22. Copenhagen: Laegemiddelstyrelsen, 1998 (in Danish).
12. Rautakorpi U-M, Huovinen P, Klaukka T. Is the duration of antibiotic treatment too long? Suom Lääkäril 1997; 52: 3228–30 (in Finnish).
13. MIKSTRA Steering Group. MIKSTRA to guide antimicrobial use in primary care. Suom Lääkäril 1998; 53: 1524–6 (in Finnish).

14. www.mikstra.fi

15. Mäkelä M. Current Care evidence-based guidelines programme. Nordic EBHC Newsl 1999; 3: 9–10.

16. Evidence based guidelines for primary bacterial skin infections, acute sinusitis, acute otitis media, throat infections, acute bronchitis and urinary tract infections. Duodecim 1999; 115: 2135–75; 2000; 116: 782–96 (in Finnish).

17. Ministry of Agriculture and Forestry and Ministry of Social Affairs and Health. Bacterial resistance to antimicrobial agents in Finland. Helsinki: FINRES, 1999. (www.mmm.fi/english/veterinary/publications)

18. Premi JN. Problem-based, self-directed continuing medical education in a group of family physicians. J Med Educ 1988; 63: 484–6.

19. Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach a randomised controlled trial of academically based 'detailing'. N Engl J Med 1983; 308: 1457–63.

20. Hermansson T, Aro S, Bennett CL. Finland's health care system: universal access to health care in a capitalistic democracy. JAMA 1994; 271: 1957–62.

21. Lauslahti K, Roine R, Semberg V, Kekomäki M, Konttinen M, Karp P. Health technology assessment in Finland. Int J Technol Assess Health Care 2000; 16: 1–18.

22. Rautakorpi U-M, Lumio J, Huovinen P, Klaukka T. Indication-based use of antimicrobials in Finnish primary health care. Description of a method for data collection and results of its application. Scand J Prim Health Care 1999; 17: 93–9.

23. Becker L, Glazier R, McIsaac W, Smucny J. Antibiotics for acute bronchitis (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software, 2000.

24. Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis. Lancet 1995; 345: 665–6.

25. Howie JGR. Further observations on diagnosis and management of general practice respiratory illness using simulated patient consultations. Br Med J 1974; ii: 540–3.

26. Kristinsson KG. Modification of prescribers' behaviour: the Icelandic approach. Clin Microbiol Infect 1999; 5: 4S43–7.

27. Shaynefelt TM, Mayo-Smith MF, Rothwangl J. Are guidelines following guidelines. The methodological quality of clinical practice guidelines in the peer-reviewed medical literature. JAMA 1999; 281: 1900–5.

28. Grol R. Personal paper: beliefs and evidence in changing clinical practise. Br Med J 1997; 315: 418–21.

Diagnostic Tools in Respiratory Tract Infections: Use and Comparison with Finnish Guidelines

PEKKA OLAVI HONKANEN[1], ULLA-MAIJA RAUTAKORPI[2,3], PENTTI HUOVINEN[2], TIMO KLAUKKA[4], ERKKI PALVA[5], RISTO ROINE[6], HANNU SARKKINEN[7,8], HELENA VARONEN[8], MARJUKKA MÄKELÄ[6] and THE MIKSTRA COLLABORATIVE STUDY GROUP*

From the [1]Department of Public Health Science and General Practice, University of Oulu, Oulu, Finland and Health Centre of Kemi, Kemi, Finland, [2]Antimicrobial Research Laboratory, National Public Health Institute, Turku, Finland, [3]Health Centre of Pirkkala, Pirkkala, Finland, [4]Social Insurance Institution, Helsinki, Finland, [5]National Agency for Medicines, Helsinki, Finland, [6]FinOHTA, the National Research and Development Centre for Welfare and Health, Helsinki, Finland, [7]Central Hospital of Päijät-Häme, Lahti, Finland and [8]Finnish Medical Society Duodecim, Helsinki, Finland

The objectives of this prospective epidemiological study were to describe the diagnosis and treatment of respiratory tract infections by Finnish general practitioners and to compare current practice with national evidence-based guidelines. All patients ($n = 4386$) seeking primary care for a respiratory tract infection for the first time in 30 health centres during 1 week in November 1998 participated in the study. The main outcome measures were the amounts and types of diagnostic tests used and antimicrobials prescribed. Tympanometry was used in 1% of patients with acute otitis media. Ultrasonography, sinus radiography or both were used in 80% of cases of sinusitis and antigen detection or culture for Streptococci in 57% of throat infections. In acute bronchitis, a chest radiograph was taken in 5% of cases and the CRP level determined in 8%. The corresponding figures for pneumonia were 49% and 39%. In pneumonia and throat infection, diagnostic testing was statistically significantly associated with the use of antimicrobials, but not in otitis, sinusitis or acute bronchitis. Diagnostic tests were underused in respiratory tract infections compared to evidence-based recommendations.

P. Honkanen, Health Centre of Kemi, Kirkkopuistokatu 1 A, FIN-94100 Kemi, Finland. Tel.: + 358 16 259680; Fax: + 358 16 259776; E-mail: Pekka.Honkanen@Kemi.fi

INTRODUCTION

Respiratory tract infections are the most common diseases encountered in primary care (1, 2) and up to 80% of all antimicrobials used in Finnish primary care are prescribed for these diagnoses (3). Annually this amounts to 3 million prescriptions in a Finnish population of 5 million (4). Some 20–50% of this use is estimated to be unnecessary (5). Reducing the use of antimicrobials is 1 of the most important methods of combating the development of resistant bacterial strains.

Acute respiratory tract infections (otitis media, sinusitis, tonsillitis, pharyngitis, bronchitis and pneumonia) and unspecified upper respiratory tract infections (common cold) are closely related and share similar symptoms, pathogenesis and aetiology (6). They can all be caused by viruses, bacteria or a combination of both. Instead of identifying the specific etiologic agent, the clinician's main problem is usually whether or not the probable agent is treatable with antimicrobials. Clinical signs are unhelpful in most cases, as they differ little between bacterial and other infections. Notable effusion of the eardrum in otitis media is usually a sign of a bacterial origin (7). In other respiratory tract infections, clinical signs and symptoms do not provide sufficient information about aetiology (8–12).

Diagnostic tests can help to achieve a more precise diagnosis than clinical findings alone. Tympanometry can be

used in otitis media, whilst in sinusitis radiography or ultrasonography are available (13, 14). In tonsillar or pharyngeal infection, the clinician can obtain a throat swab to test for Streptococci (12). The signs of infection of pulmonary tissue in pneumonia can be seen by means of chest radiography and, in bronchitis, the CRP level is higher in bacterial than in viral infections (15, 16). These diagnostic tools are recommended for use in respiratory tract infections in recent Finnish guidelines (17–20). The frequency with which these tools are used reflects the quality of the professional diagnostic and decision-making processes. In this epidemiological study we surveyed the use of diagnostic tools among Finnish general practitioners prior to publication of the guidelines so as to establish baseline data for a trial of implementation of the guidelines.

MATERIAL AND METHODS

In 1997 we asked all Finnish health centres ($n = 217$) about their willingness to participate in a trial concerning changing the management of common infectious diseases towards a more evidence-based direction. Of 82 health centres that expressed an interest, 30 were enrolled in the study. These health centres were selected as being representative of the whole country regarding setting (rural or urban), size and geographical location. The population covered by these health centres is 820,000 (16% of the Finnish population).

During 1 week in November 1998, the physicians and nurses collected data on every patient attending for an infectious disease consultation on a structured case report form. Data collected were: patient age and gender; the main diagnosis; use of diagnostic tools; prescription of antimicrobial and other medications; and numbers of consultations during this infectious episode. The case report

---

forms were mailed to the study office at Stakes (National Research and Development Centre for Welfare and Health). The data were processed using SPSS for Windows software.

RESULTS

Data were received on 7964 consultations, of which 74 were excluded because the diagnosis was not an infectious disease and 95 for missing diagnoses. Of the 7777 infectious disease cases, 6121 (79%) were first consultations and 4386 of these were due to a respiratory tract infection. Of these 4386 patients, 57% were women and 23% were ≤ 5 y old (Table I).

Some diagnostic test was used in 40% of all cases and the use of tests varied remarkably between diseases (Table II). In acute otitis media, tympanometry was used in only 8/915 cases (1%). In sinusitis, ultrasonography, sinus radiography or both were carried out in 80% of cases. Throat culture, antigen detection or both were obtained in 57% of throat infections. In acute bronchitis, a radiograph was taken in 5% of patients, the white blood cell count (WBC) determined in 5% and CRP was assayed in 8%. The corresponding figures in pneumonia were 49%, 27% and 39%. In pneumonia, both chest X-ray and CRP determination were performed in 32%.

Antimicrobials were prescribed in 51% of all acute respiratory tract infections. Most antimicrobials were used for acute otitis media (38%) and sinusitis (26%). Overall, antimicrobials were given to 52% of those who had been tested and to 51% of those not tested ($p = 0.589$). When the association of the use of diagnostic tests and prescriptions was analysed in more detail, the management patterns were found to vary

by diagnosis. In pneumonia, 87% of those tested with chest radiography or WBC or CRP determinations received antimicrobials, compared to only 50% of those not tested ($p = 0.016$). In bronchitis, the corresponding figures were 64% and 73% for the tested and non-tested patients, respectively ($p = 0.215$). In throat infections, antimicrobials were prescribed to 41% of patients tested with either antigen detection or culture, compared to 50% of those not tested ($p = 0.015$). In sinusitis, 89–90% of patients received antimicrobials regardless of testing ($p = 0.878$). The use of diagnostic tests by age group is presented in Table III.

DISCUSSION

The use of diagnostic tests was most frequent (81%) in sinusitis and least frequent in acute otitis media (8%). Comparing the use of tests with the recommendations in the recently published Finnish evidence-based guidelines for otitis, sinusitis, tonsillitis and bronchitis (17–20), the guideline tests were clearly underutilized as support for treatment decisions (Table IV). Only in sinusitis were the tests used nearly as recommended.

In children aged < 5 y, diagnostic tests were used statistically significantly less than in other age groups for acute otitis media, acute bronchitis, pneumonia and upper respiratory tract infection. Of 7 children with pneumonia in the < 5 y age group, 4 were referred to hospital without any further diagnostics being done. The diagnoses of acute otitis media, acute bronchitis and upper respiratory tract infection may be clearer in this age group, so that the diagnostic alternatives

Table I. *The number of cases of each respiratory tract infection and the distribution of patients by age and gender*

Diagnosis	No. of cases (%)	Percentage of males	Percentage of patients in each age group (y)			
			<5	5–14	15–64	≥65
Otitis	915 (21)	50	51	32	16	1.6
Throat infection	754 (17)	39	9	22	67	2.1
Sinusitis	670 (15)	33	2	12	79	7.3
Acute bronchitis	429 (10)	45	18	14	57	11
Pneumonia	41 (1)	51	17	15	54	15
Upper respiratory tract infection	1577 (36)	43	25	19	53	2.9
All	4386	43	23	21	52	4

Table II. *The use of diagnostic tools in respiratory tract infections. The values represent the percentage of patients undergoing each diagnostic test*

Diagnosis	Any test	WBC	CRP	Throat culture	Throat antigen detection	Chest X-ray	Sinus X-ray	Sinus ultra-sonography
Otitis	8	1	1	1	2	0	0	3
Throat infection	67	2	5	37	24	1	0	7
Sinusitis	81	2	2	1	1	2	5	74
Acute bronchitis	29	5	8	1	1	5	1	19
Pneumonia	61	27	39	5	5	49	7	5
Upper respiratory tract infection	30	4	7	7	3	2	2	15

Table III. *The use of any diagnostic test (%; with 95% confidence interval in parentheses) among persons with a respiratory tract infection in each of 4 age groups*

Diagnosis	Age group (y)			
	<5	5–14	15–64	≥65
Otitis	4 (2–6)	9 (6–12)	20 (13–26)	27 (8–55)
Throat infection	54 (41–66)	68 (60–75)	69 (65–73)	56 (30–80)
Sinusitis	60 (26–88)	77 (66–86)	83 (80–86)	69 (55–82)
Acute bronchitis	8 (3–16)	28 (17–41)	35 (29–41)	31 (18–45)
Pneumonia	0	33 (4–78)	77 (55–92)	100 (54–100)
Upper respiratory tract infection	10 (7–13)	36 (30–41)	38 (35–41)	38 (35–41)

Table IV. *Comparison of Finnish evidence-based clinical guidelines for 4 respiratory tract infectious diseases and routine clinical management of general practitioners*

Disease	Methods of diagnosis according to guidelines	Use of a relevant test by general practitioners	Comparison between practice and recommendations
Otitis	Detection of middle ear effusion with pneumatic othoscope completed by tympanometry	Tympanometry 1%	Notably underused
Throat infection	Detection of Streptococcus A by antigen detection or culture	Culture 37%, antigen detection 24%	Slightly underused
Maxillary sinusitis	Symptoms of acute upper respiratory tract infection and detection of maxillary effusion by ultrasonography or X-ray	X-ray 5%, ultrasonography 74%	Correct
Bronchitis	Clinical symptoms and signs completed by determination of CRP	CRP determination 8%	Notably underused

are fewer and differential diagnostic tests are needed less frequently than in the older age groups.

The key decision in common respiratory tract infections is whether to prescribe antimicrobials. In order to be useful, a diagnostic test must influence prescribing. In 40% of infections, the use of diagnostic tools was associated with antimicrobial prescribing. In throat infections, testing was associated with less frequent use of antimicrobials, whereas in pneumonia the opposite association was observed. The results of the diagnostic tests used were not recorded in the case report forms, which limits conclusions about the guiding effect of the use of diagnostic tests towards correct antimicrobial prescription. In 2 previous studies the guiding effect of tests was found to be poor (21, 22). The diagnostic process is neither entirely rational nor based on biomedical factors alone: determinants such as workload, social pressure and fear of complications also guide the decision-making process (23). When patients are not tested systematically, physicians may either test to avoid antimicrobial treatment (as in tonsillitis in our study) or to reliably recognize a serious disease (as in pneumonia).

The diagnoses of otitis media and maxillary sinusitis are established by detecting effusion in the middle ear and maxillary sinus, respectively. Finnish guidelines suggest that these diseases should be treated with antimicrobials if effusion is present. The correct use of antimicrobials in sinusitis

requires that the clinician can interpret the ultrasonographic and radiographic findings reliably. In otitis media, more frequent use of tympanometry could lead to more accurate diagnosis and help a clinician to target antimicrobial treatment to those who would benefit most from it. In our material, tympanometry was too seldom used to test this hypothesis. The seriousness of the clinical picture seems to influence both test ordering and antimicrobial prescription, but the direction of this influence varies.

In Nordic countries, although guidelines are equivalent in most aspects some differences do exist. In Norwegian and Swedish recommendations, follow-up without antimicrobial treatment is the first choice in patients aged ≥ 2 y with acute otitis (24, 25), but in Finnish guidelines medication is preferred (20). In throat infection, Swedish guidelines rely on clinical diagnosis of Streptococcus pyogenes if 4/4 diagnostic criteria are fulfilled (26). According to Finnish guidelines microbiological diagnosis is always recommended (17). The clinical practice patterns observed in this study are representative of Finnish primary care and are thus generalizable to Finland. Treatment patterns vary from country to country, but problems related to the management of respiratory tract infections are international. Our study demonstrates that everyday routine is very different from evidence-based recommendations for the treatment of common respiratory tract infections.

Guidelines are necessary, and efficient ways of implementing them in everyday practice should be searched for. One means of measuring the success of the implementation of guidelines may involve monitoring the association of positive and negative test results with the use of antimicrobials.

CONTRIBUTORS

The members of the MIKSTRA Collaborative Study Group are as follows: The members of the MIKSTRA Collaborative Study Group are as follows: Irja Laaksonen, Asikkala Health Centre; Markku Kanerva, Tapiola Health Centre, Espoo; Anne Niemelä, Haapavesi Health Centre; Timo Virtanen, Hamina Health Centre; Liisa Toppila, Alppiharju Health Centre, Helsinki; Camilla Mårtenson, Latokartano Health Centre, Helsinki; Kari Penttilä, Inari Health Centre; Marjatta Kaitila, Joutseno Health Centre; Jarmo Lappalainen, Juva-Puumala-Sulkava Health Centre; Jarmo J. Koski, Jyväskylä City Health Centre; Anu Kurikkala, Kannus Health Centre; Timo Kankaanpää, Muurame Health Centre, Korpilahti; Matti Norja, Kyrönmaa Health Centre; Antti Salmio, Tuulos Health Centre, Lammi; Sirkka-Liisa Hiltunen, Masku Health Centre; Esko Nukari, Mäntsälä Health Centre; Kauko Koivisto, Mänttä Health Centre; Esa Asikainen, Nilsiä Health Centre; Olli Sipilä, Oulu Health Centre; Jouko Hietala, Pirkkala Health Centre; Antti Piiroinen, Rovaniemi City Health Centre; Pasi Tonteri, Rovaniemi Health Centre; Seppo Junnila, Salo Health Centre; Markku Valli, Seinäjoki Health Centre; Marja-Liisa Laitinen, Suomussalmi Health Centre; Maarit Karppinen, Tohmajärvi Health Centre; Eero Vaissi, Turku Health Centre; Kyösti Lemmetty, Ulvila Health Centre; Marketta Klemola, Valkeakoski Health Centre; and Risto Kettunen, Varpaisjärvi Health Centre.

REFERENCES

1. Kirkwood C, Clure H, Brodsky R, Gould G, Knaak R, Metcalf M, et al. The diagnostic content of family practice: 50 most common diagnoses recorded in the WAMI community practice. J Fam Pract 1982; 15: 485–92.
2. Kokko S. Tauti ja sairaus-työikäiset terveyskeskuslääkärin vastaanotolla. University of Kuopio: Kuopio, 1988.
3. Rautakorpi U-M, Klaukka T, Lehtomäki J, Lumio J. Mikrobilääkkeiden käyttö tutkittiin Pirkanmaalla. SuomLääkl 1995; 50: 1121–7.
4. Rautakorpi U-M, Lumio J, Huovinen P, Klaukka T. Indication-based use of antimicrobials in Finnish primary health care. Scand J Prim Health Care 1997; 17: 93–9.
5. Wise R, Hart T, Cars O, Streulens M, Reinen H, Huovinen P, et al. Antimicrobial resistance is a major threat to public health. Br Med J 1998; 317: 609–10.
6. Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. Br Med J 1997; 315: 1060–4.
7. Bluestone C, Stephenson J, Martin LM. Ten-year review of otitis media pathogens. Pediatr Infect Dis 1992; 11: 507–11.
8. Williams J, Simel D. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. JAMA 1993; 270: 1242–6.
9. Bisno A, Gerber M, Gwaltney J, Kaplan E, Schwartz R. Diagnosis and management of group A Streptococcal pharyngitis: a practice guideline. Clin Infect Dis 1997; 25: 574–83.
10. Nohynek H, Valkeila E, Leinonen M, Eskola J. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. Pediatr Infect Dis J 1995; 14: 484–90.
11. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 1997; 287: 1440–5.
12. Ebell M, Smith M, Barry H, Ives K, Carey M. Does this patient have strep throat? JAMA 2000; 284: 2912–8.
13. Koivunen P, Alho O-P, Uhari M, Niemelä M, Luotonen J. Minitympanometry in detecting middle ear fluid. J Pediatr 1997; 131: 419–22.
14. Varonen H, Mäkelä M, Savolainen S, Läärä E, Hilden J. Comparison of ultrasound, radiography, and clinical examination in the diagnosis of acute maxillary sinusitis: a systematic review. J Clin Epidemiol 2000; 53: 940–8.
15. Babu G, Ganguly NK, Singhi S, Walia BNS. Value of C-reactive protein concentration in diagnosis and management of acute lower respiratory infections. Trop Geogr Med 1989; 41: 309–15.
16. Örtqvist Å, Hedlund J, Wretlind B, Carlström A, Kalin M. Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia. Scand J Infect Dis 1995; 27: 457–62.
17. Suomen Mikrobiologit ry. Nielutulehduksen hoitosuositus. Duodecim 1999: 2162–7.
18. Suomen Otolaryngologiyhdistys ry. Äkillisen poskiontelotulehduksen hoitosuositus. Duodecim 1999: 2147–53.
19. Suomen Yleislääketieteen yhdistys ry. Äkillisen keuhkoputkitulehduksen hoitosuositus. Duodecim 1999; 115: 2171–5.
20. Puhakka H, Hagman E, Heikkinen T, Huovinen P, Jero J, Karma P, et al. Äkillisen välikorvatulehduksen hoitosuositus. Duodecim 1999: 2155–61.
21. Mäkelä M. Rapid throat-culture as diagnostic aid: ineffective in decreasing antibiotic prescription. Scand J Prim Health Care 1987; 5: 145–50.
22. Melbye H, Aaraas I, Fleten N, Kolstrup N, Mikalsen J-I. Nytten av å teste C-reaktivt protein ved mulig nedre luftveisinfeksjon. Tidskr Nor Lægeføren 1995; 115: 1610–5.
23. Howie J. Some non-bacteriological determinants and implications of antibiotic use in upper respiratory tract illness. Scand J Infect Dis Suppl 1983; 39: 68–72.
24. Berild D, Digranes A, Hjordal P, von der Lippe E, Mellbye H, Ringertz S. Antibiotika i allmennpraksis [cited 2002 June 7]. Available from: http://www.helsetilsynet.no/trykksak/ik-2693/aotitis.htm
25. Konsensusuttalande. Behandling av akut öroninflammtion hos barn. Medisiniska forskringsrådet [cited 2002 June 7]. Available from: http://www.mfr.se/publicationer/index.asp
26. Handläggning av Faryngotonsilliter – Rekommendationer. Info från Läkemedelsverket 7/8 2001; 12: 44–75.