



Consumption of antibacterial agents

- pharmacoepidemiology, resistance and interventions

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Contents

1	Acknowledgements	4
2	List of papers	5
3	Abbreviations	6
4	Introduction	7
	<i>4.1 Describing consumption of antibacterial agents</i>	<i>7</i>
	<i>4.2 Consumption of antibacterial agents – regional and national differences</i>	<i>10</i>
	<i>4.3 Determinants for the consumption of antibacterial agents</i>	<i>13</i>
	<i>4.4 Consumption of antibacterial agents and emergence of resistance</i>	<i>17</i>
	<i>4.5 Interventions to change suboptimal usage of antibacterial agents</i>	<i>21</i>
5	Aims	25
6	Methods	27
7	Summary of papers and main results	31
8	Discussion	37
	<i>8.1 Acute otitis media</i>	<i>37</i>
	<i>8.2 Enterococcal resistance to ampicillin, gentamicin and vancomycin and use of antimicrobials in five Nordic hospitals</i>	<i>43</i>
	<i>8.3 Clostridium difficile associated diarrhea in two university hospitals</i>	<i>49</i>
	<i>8.4 Validation of a simplified netilmicin dosage regimens in infants</i>	<i>51</i>
9	Further aspects	54
10	References	55

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2 List of papers

Paper I

Småbrekke L, Berild D, Giæver A, Myrbakk T, Fuskevåg A, Ericson JU, Flægstad T, Olsvik Ø, Ringertz SH. Educational intervention for parents and healthcare providers leads to reduced antibiotic use in otitis media. *Scand J Infect Dis* 2002; 34(9): 657-9.

Paper II

Simonsen GS, **Småbrekke L**, Monnet DL, Sørensen TL, Møller JK, Kristinsson KG, Lagerqvist-Widt A, Torell E, Digranes A, Harthug S, Sundsfjord A. Prevalence of resistance to ampicillin, gentamicin and vancomycin in *Enterococcus faecalis* and *Eterococcus faecium* from clinical specimens and use of antimicrobials in five Nordic hospitals. *J Antimicrob Chemother* 2003; 51(2): 323-31.

Paper III

Berild D, **Småbrekke L**, Halvorsen DS, Lelek M, Stahlsberg EM, Ringertz SM. *Clostridium difficile* infections related to antibiotic use and infection control facilities in two university hospitals. *J Hosp Infect* 2003; 54(3): 202-6.

Paper IV

Klingenberg C, **Småbrekke L**, Lier T, Flægstad T. Validation of a simplified netilmicin dosage regimen in infants. *Scand J Infect Dis* 2004; 36(6-7): 474-9.

3 Abbreviations

AC	Antibiotic cycling
AOM	Acute otitis media
C_{\min}	Serum concentration, minimum
CDSS	Computerized decision support system
CPR	Central population registry
CRP	C-reactive protein
DDD	Defined daily dose
DID	DDD/1000 inhabitants/day
DOT	Days of therapy per time period
ECS	Emergency call service
GA	Gestational age
HLGR	High level gentamicin resistance
INN	International non-proprietary name
ITS	Interrupted time series
MEF	Middle ear fluid
MIC	Minimum inhibitory concentration
NCCLS	National committee for clinical laboratory standards
NorPD	Norwegian prescription database
PA	Postnatal age
PenV	Penicillin V (phenoxymethylpenicillin)
PFGE	Pulse field gel electrophoresis
PMA	Post menstrual age
RTI	Respiratory tract infections
SNC	Serum netilmicin concentration
UK	United Kingdom

4 Introduction

4.1 Describing consumption of antibacterial agents

Antibacterial agents are among the most frequently used drugs worldwide, and contribute immensely to human and animal health. However, the consumption of antibacterial agents is closely linked to emergence and spread of resistance in commensal and pathogenic species (1, 2). A high prevalence of resistance in human pathogens is associated with a detrimental outcome and increased costs in the treatment of infectious diseases (3). Mathematical modeling and epidemiological observations suggest that the emergence of resistance caused by constant selective pressure from antibacterial agents evolves more rapidly compared to the decay time after a decline in the consumption (4, 5). The rational use of antibacterial agents is increasingly recognized as an important contribution to control the worldwide emergence of bacterial resistance, to minimize side effects and to reduce the cost of treatment (6-8). Knowledge on how antibacterial agents are being prescribed and used is fundamental to obtain rational drug use. Information of the past performance of prescribers and consumers is the pillar in all auditing systems (9). Consumption of antibacterial agents can be described at an ecological level, where information on the identity of the consumer and individual consumption is unavailable, or at an individual level where such information is assessed.

The ecological level

The concept of describing consumption of antibacterial agents at an ecological level must address; i) the profile of therapy, ii) the extent of consumption, and iii) the trends in consumption over time. The profile of therapy is precisely described by using the International Non-proprietary Name (INN), which is a unique and internationally recognized identification of an active pharmaceutical substance. Non-proprietary names are public property, and are synonymous to generic names (10).

To describe the extent of consumption is a more complex exercise, with several nominators and denominators available. In addition, it is also necessary to consider consumption among outpatients differently from consumption in hospitals or other variants of institutional care.

Outpatients consume approximately 85 - 93% of the total volume of antibacterial agents, a proportion which depends on the organization of health care services and the availability of institutional health care on national level (11, 12). The consumption

among outpatients has been expressed in physical units (mass or volume), the number of packages, tablets or ampoules, the proportion of prescriptions with antibacterial agents, the number of patient's days on an estimated clinical dose, or as a defined daily dose (DDD). The DDD for an active pharmaceutical substance is the average maintenance dose used for its major indication in adults (9). All units except the proportion of prescription with antibacterial agents are normally adjusted for the population under risk over a given time period, usually expressed per 1000/inhabitants/day (DID). For some agents there is a considerable discrepancy between DDD and the actual clinical dose. The DID is therefore only a rough estimate of the proportion of the population under treatment. DDD's are revised over time, necessitating recalculation of consumption data in time trend analysis when long time periods are considered. Divergent versions of the ATC/DDD system have been shown to cause methodological problems when comparing national consumptions (13). Despite several other limitations, the DID is the WHO recommended method for monitoring outpatient use of antibacterial agents. The trends in drug consumption are important sources of information, and can contribute to the understanding of changing drug costs, and possibly identify regional differences and suboptimal use of antibacterial agents. To uncover trends in the consumption of antibacterial drugs amongst outpatients requires access to longitudinal data, preferably collected over several years. For example, longitudinal data on the consumption of antibacterial agents in Norway show an increase over the last eight years (14). This increase can not be explained by changes in the panorama of infectious diseases, the prevalence of resistant strains, or the age structure of the population (15).

In hospitals, the extent of consumption has been expressed in physical units per bed or per bed day for a given time period, or as DDD/100 bed days/year or DDD/100 admissions/year, or as days of therapy per time period (DOT) (16-19). DDD adjusted for bed days has been the recommended method for monitoring hospital use of antimicrobial agents, but this denominator has limitations when the number of admissions per time unit or the average staying time in the hospital changes over time (17, 18). An increasing number of admissions will always result in increased consumption, especially if the rise in admissions parallels a higher frequency of invasive procedures. For example, the average consumption of antibacterial agents expressed as DDD/100 bed days/year in a selection of Dutch hospitals increased by 24% to 62,2 DDD/100 bed days/year over the years 2002 – 2006. Over the same period the number of DDD/100 admissions/year remained almost constant; 336,5 in 2002 versus 335,8 in 2006 (20). Neither denominator indicates the number of patients

or the proportion of patients receiving antimicrobial therapy, but both methods should be considered when assessing compliance to clinical guidelines.

The individual level

At the individual level, information on; i) indication, ii) the choice of therapy, iii) the dosage, iv) the duration of treatment, v) the route of administration, and vi) the timing of the treatment may be necessary to answer important clinical questions and to give correct interpretation of the data. Also in this context it is necessary to consider consumption among outpatients differently from consumption in hospitals or other variants of institutional care.

For outpatients, access to longitudinal data is important in the development of quality indicators on medical treatment and in planning interventions to optimize drug use (21). Until 2004, there were no systematic collections of national data on individual drug consumption amongst outpatients in Norway. From the 1st of January 2004, all pharmacies have been obliged to submit data to the Norwegian Prescription Database (NorPD) (22). The identity of the patient is encrypted, but a unique identifier derived from the Central Population Registry (CPR) enables the tracking of all prescriptions to a patient over time. Prescription databases are also established in the other Nordic countries, although with different possibilities to extract longitudinal data for individuals. Similar entities are not established in other parts of the world. Other sources of individual drug consumption amongst outpatients are interviews or questionnaires as parts of population based health surveys. Comprehensive surveys may also contain valuable information on clinical data, risk factors, and other variables that are associated with the consumption of antibacterial agents. However, these data sources can never be a substitution for a national prescription database decreed by law.

In hospitals, the patient journal should ideally contain all relevant data on drug consumption, but such data are not always available (own observation, unpublished). In addition such data are readily accessible only if the complete journal is in electronic format, but electronic patient journals with information on drug consumption are not common in the Nordic countries. Access to data describing both individual consumption of antibacterial agents and resistance emergence in the bacterial pathogen infecting the same individual will provide a better understanding of the temporal relationship between consumption and resistance (16, 23).

4.2 Consumption of antibacterial agents – regional and national differences

Systematic data on the profile and extent of use of antimicrobial agents at the national level is publicly and easily available only in a few developed countries and are scarce or non-existing in most developing countries. Possible sources of information on national use are reimbursement data based on financial claims from legitimate beneficiaries, from prescribers or pharmacies, or sales data from pharmaceutical companies, wholesalers, pharmacies or marketing research companies. The validity of such data may be affected by coverage bias in census data, sampling bias in sample data, unaccounted sales over the counter in reimbursement data, parallel trade, erroneous registration of non-reimbursed sale, and bias due to a mix of antibiotic use between hospital and ambulatory care (24-28). Most longitudinal data addressing consumption of antibacterial agents at a national level is aggregated and gives no information on individual consumption or how consumption is distributed over age groups.

There is an abundance of data addressing regional differences within countries in choice of antibacterial therapy and the extent of consumption for outpatients, and also for differences between hospitals with similar patient populations (29-36). Most of these studies are descriptive and are thus unsuitable to elucidate the causal factors behind the observations.

North-America, Canada and Australia

The consumption in USA (25,5 DID) is higher than the average consumption in Europe, and there is a trend towards an earlier shift to newer agents in the USA (37). It is highly probable that the consumption varies between states and regions in choice of therapy and in amount of consumption, but comprehensive information on this matter is unavailable. In Europe, only Greece, France, Italy and probably Spain have higher consumption than USA.

In Canada, the average consumption is approximately 10% lower (22,5 DID) than in the USA, although there are some data indicating regional differences. For example in British Columbia, the consumption was reduced from 19,5 DID in 1996 to 17,9 DID in 2000, clearly below the Canadian average (28).

In Australia the average consumption declined from 24,8 DID in 1995 to just over 21 DID in 2002 (38, 39). This reduction is possibly related to a national campaign promoting appropriate use of antibacterial agents against respiratory tract infections (39).

Interestingly, the number of active antibacterial substances available is lower in the USA compared to the European markets, 81 and 157, respectively.

Europe

The data for year 2003 show considerable variation in out-patient use of antibacterial agents in Europe with more than a 3-fold higher consumption in Greece with 31,4 DID than in the Netherlands with 9,8 DID (26). There are also examples of rapid changes in consumption over short periods. For example, during the period from 2001 to 2006 the consumption of antibacterial agents in Turkey more than doubled from 14,6 DID to 31,4 DID, the largest increase taking place after the implementation of social insurance reform in 2005. In Turkey, 24% of the total annual expenditure for pharmaceuticals was spent on antibacterial agents in 2002. There is also a considerable variation in choice of therapy as the proportion of the consumption made up of cephalosporins, macrolides and quinolones is higher in southern Europe than in Scandinavia and other countries in northern Europe. The proportion of the consumption made up of narrow spectrum penicillins is higher in Scandinavia than in southern Europe (12, 25, 28, 36, 40-44). In the European markets there is an association between the numbers of antibacterial substances available for oral use and the consumption of these agents amongst outpatients (45). A high number of available substances correlated with a high level of consumption.

The interpretation of sales data from some European low cost countries is highly complex because the high extent of parallel trade with exports to countries with higher medicine prices is poorly described. Based on data from wholesale only, the data for Greece include both national consumption and quantities for parallel export, and is therefore probably an overestimation of the actual use (12, 25).

Although legislation in all European countries state that a patient in ambulatory care needs a prescription for antibacterial agents, it is well known that in some countries patients are allowed to buy antibacterial agents over the counter. If the national estimate on antibacterial use is based on reimbursement data, this will underestimate the true sale because there is no reimbursement on sales without prescription.

The rate of self-medication in Europe varies between 1 and 220 per 1000 inhabitants/year, but may be higher in certain populations. Rates are high in eastern- and southern Europe and low in western- and northern Europe. Sale of antibacterial agents without prescription over the counter in Spain represents up to 30% of the total consumption, and the most frequently used antibiotics for self-medication are broad

spectrum penicillins and macrolides (46-51). Data from other parts of the world also indicate frequent self-medication with antibiotics (52-54).

For Europe, seasonal variations in the use of antibacterial agents with high consumption in the first and fourth quarter of the year, is a well documented phenomenon related to increased incidence of respiratory tract infections. However, the seasonal variation is most excessive in high consuming countries (25, 55-59). As a high proportion of respiratory tract infections are self-limiting and of viral origin, a high versus a small mean difference in consumption between winter and summer months suggests inappropriate prescription practice or high level of self-medication (25).

The Nordic countries

Wholesale statistics on antibacterial agents for the Nordic countries is comprehensive. For the year 2007 the consumption (not counting metenamin) was lowest in Sweden (15,5 DID) and highest in Iceland (23 DID) (11). Other striking differences are the high relative consumption of quinolones in Finland and Sweden, the high relative consumption of cephalosporins in Finland, and the low consumption of tetracyclines in Denmark. Interestingly, tetracyclines are not reimbursed in ambulatory care in Denmark.

The Norwegian Prescription Database covers all prescriptions collected at Norwegian pharmacies, and allows longitudinal studies on drug use in individuals (22). A study covering one year found the mean yearly population prevalence of antibacterial use to be 28% and 19%, for females and males, respectively (60). The choice of therapy differed between gender and age groups. Persons under 5 and over 75 years were high consumers. High consumers, defined as those using more than 60 DDD/year, amounted to 3% of the population using antibacterial agents.

4.3 Determinants for the consumption of antibacterial agents

Health related behaviors are complex, and a discussion on the determinants for the consumption of antibacterial agents must take into consideration not only the perspective of the consumer, but also the perspective of the provider in addition to marketing and regulatory affairs (61). It is also necessary to distinguish between determinants characterizing use at individual or at societal level for use amongst outpatients, as well as determinants for use in hospitals or other facilities of institutional care. The contribution to the use of antibacterial agents from determinants at the individual and societal level amongst outpatients is probably not independent, and if possible both levels should be addressed simultaneously.

Outpatients

The majority of data on determinants for the use of antibacterial agents amongst outpatients originate from retrospective studies extracting data from patient records or from prospective studies collecting data via questionnaires or interviews from patients or physicians (33, 61-70). Studies extracting data from patient records often address a particular patient group, and this of course limits the external validity of the studies. However, these data are important as a fundament for building hypotheses when trying to explain the large differences in consumption and choice of therapy that, for example, are observed between European countries.

Collecting data by sending questionnaires to a representative sample of a population is an attractive approach to gain information on determinants for the use of antibacterial agents, but the validity of the results is heavily dependent on the response rate. Studies collecting data from different European countries have documented considerable variation in response rate (61).

At the national level, determinants for consumption of antibacterial agents amongst outpatients include the incidence and panorama of community acquired infections, culture- and social conditions, statutory practice, health care structures, spending power of the patients, level of self-medication, governmental regulations including market regulations and reimbursement policy, national guidelines and the number of different antibacterial substances marketed and trade names available (45, 61-64, 70, 71). Possibly, national guidelines on treatment of common infectious diseases may have an important function as frameworks for local initiatives. There are a diversity of

promotional actions from the pharmaceutical industry, although their relative importance seems to be dependent on the type of drug (72).

At the individual level, determinants for the consumption of antibacterial agents are availability of health care, spending power, level of self-medication, patient-doctor relations, marketing and knowledge about the effects and adverse effects of antimicrobial agents (63, 64, 73-76). The latter is exemplified by data from a study from the USA on misconceptions on prudent and appropriate use of antibacterial agents (77). Almost half of the interviewed patients were unaware of possible consequences of skipping doses and that antibacterial agents have no effect against viral infections. The providers stated that they prescribed antibacterial agents on patient demand. A majority of the patients were aware of resistance as a phenomenon, but only one-third considered resistance to be common.

Similar trends were found in a study from Wales (78). Amongst patients, perceived importance and personal threat with regard to resistance were low, and less than 25 % of the respondents considered they could affect the threat of emerging resistance by correct use of antibacterial agents or to refrain from prescriptions. Another study, also from Wales, found that general practitioners were concerned about microbial resistance but infrequently faced problems with resistance in daily practice (79). Some of the respondents questioned the evidence linking their prescribing to possibly poorer future outcomes for their patients, and a few mentioned that increased awareness on resistance may enhance the use of second line empirical therapy.

In a study from USA including generalists and infectious disease specialists, both groups preferred newer and broader spectrum agents against community acquired pneumonia compared to older agents still advised by national guidelines. The physicians rated the issue of possible contribution to the development of resistance lowest among seven determinants for their choice (80).

In a Swedish study addressing the use of medical care and antibiotics amongst children aged 6-15 years, the investigators found that children of parents with less than 10 years of education consumed less antibiotics than children of parents who had completed secondary school or longer education. They also found that children in rural areas consulted physicians more seldom and consumed less antibiotics compared to children in big cities (81). Due to the design of the study, it was impossible to explain the causal relationship behind these observations.

The above examples illustrate potential conflicts between balancing long-term societal and public health interests (reserving new and broad spectrum agents for severe infections and future use) and the short-term immediate interest of the individual (highest possible probability for cure).

Hospitals

The panorama of infectious diseases, local profile of bacterial resistance, the proportion of patients undergoing surgery and the proportion of total bed days spent in the intensive care unit are important determinants for the consumption of antibacterial agents in hospitals. Some concern has also been raised that downsizing of the nursing work force and interventions towards hospital restructuring may negatively affect patient risk for infectious diseases (82). In addition there are data indicating that university hospitals and increasing bed occupancy rates are associated with increased use of antibacterial agents. However, the data on the significance of hospital size on the consumption of antibiotics are conflicting (30, 32, 36, 83, 84).

Supervisors are considered to be strong opinion leaders and are highly influential on choice of therapy, especially towards residents and inexperienced doctors. The role of other actors is less clear, but the availability of microbiologists and clinical pharmacists may be of importance (85). Some data indicate that the presence of infectious disease specialist or a multidisciplinary infectious disease team is important when making the decision on choice of therapy for severe infections (86). A hospital formulary on treatment of infectious diseases may have a major impact on antibiotic stewardship and in optimizing antibiotic therapy (87-91), although non-adherence to own guidelines is not uncommon (92). However, there are some concerns that a strict implementation of a hospital formulary may actually increase the evolution of resistant strains in a hospital due to high homogeneity in the choice of treatment (93-95).

Local guidelines may be more specific and adjusted to local therapeutic traditions, pattern of resistance and healthcare acquired infections on choice of therapy than national guidelines. However, local guidelines will meet the same barriers as national guidelines upon implementation in the hospital (85). A successful implementation of a local guideline depends on factors like distribution (easy access to electronic and paper versions), keeping the guidelines up to date, and a certain level of completeness on important diseases. Different medical disciplines have different priorities on the content of a guideline. Internal medicine residents want a high level of completeness,

while surgeons are more likely to appreciate conciseness and ease of use (85). The occurrence of non-adherence to local guidelines is well known, but the level is poorly described.

The presence of restrictions on use of certain substances, systematic reassessment of treatment after 72 hours and nominative (pre-filled) delivery forms affects the choice and length of therapy, but not the decision whether to treat or not to treat (84, 96). Some studies have found computerized decision support systems (CDSS), when allowing for calibration to the local pattern of resistance, to prescribe appropriate empirical treatment significantly more frequent than physicians (97, 98). The treatment suggested by decision support systems lowered the length of hospital stay, lowered the total costs for antibacterial agents and diminished probable future costs due to lower future resistance. However, the role for CDSS is not unambiguous, and recent communications have raised questions on the safety of electronic prescribing systems as new types of errors may be introduced (99). Such errors include misconceptions through erroneous use of the software, automation and cognitive biases.

Local impact and consequence of marketing from pharmaceutical industry is not well documented for the hospital setting, but there are some data indicating possible importance of marketing initiatives. An interesting example is the increase in the use of amoxicillin in combination with a beta-lactamase inhibitor in the Netherlands in the early 1990's (101, 102). With poorly documented advantage over amoxicillin alone considering the profile of resistance in the Netherlands, the consumption of this combination increased three-fold within hospitals over a period of five years from 1991, mostly due to increased use in prophylactic regimens and against respiratory tract infections.

Although the impact of guidelines or formularies on the outcome of treatment of infectious diseases like urinary tract infections, community acquired pneumonia and skin and soft tissue infections is well documented, it is less clear whether such guidelines also affect the decision to treat or not to treat. This may be due to the fact that guidelines or formularies seldom give extensive support for diagnostic decisions.

4.4 Consumption of antibacterial agents and emergence of resistance

Emergence of resistance to antibacterial agents is an unavoidable side-effect of consumption, and different types of data strongly support a causal relationship between consumption and the proportion of resistant bacterial strains at the individual level and at an aggregated level (4, 100-104). The evidence for this relationship builds on plausible biological explanations, concomitant variation, consistent associations over several studies, and demonstration of a dose – response relationship (105).

The consumption of antibacterial agents is the major determinant for bacterial resistances in a defined ecological system like a hospital, but simultaneous influence from other factors are also of importance. Not taking into account confounding variables including non-adherence to infection control routines, use of other antibacterial agents than the one under study, low statistical power, complex bacterial population structures and dynamics and selection bias, may explain why some investigators have failed to establish a relationship between consumption and resistance (106).

There is an abundance of studies addressing the correlation between the consumption of antibacterial agents and the level of resistance in a variety of bacterial species at the institutional level, although this is strictly no proof of a causal relationship. In addition, many studies describe a complex epidemiological situation with simultaneous efforts towards a reduction in consumption of certain antibacterial agents and intensified infection control efforts, making it difficult to attribute cause and effect to either measure.

Fewer investigators have applied more sophisticated analytical methods such as multiple linear regression models or time series and transfer function modeling to investigate this relationship. In time series, consecutive observations are fitted to a mathematical model to predict future behavior of the series trying to explain its characteristics as well as the contributing factors. The method is valid when measurements are made at equal time intervals, and these intervals are much shorter than the study period. Transfer functions are an extension of this method that allows mathematical assessment of the relationship between one or several time series. The application of time series and transfer function modeling may give an estimate of the temporal relationship between consumption and resistance, take consumption of several antibacterial agents into account, and quantify the effect on resistance (106).

Unnecessary and extended use of broad spectrum antibacterial agents is associated with increasing levels of resistant strains (107-112). Traditionally the Scandinavian approach to treatment of infections has been quite conservative compared to other parts of the world. This has conserved the effect of old antibacterial agents where an initial conservative start of treatment has been followed by a switch to broad spectrum therapy for non-responders. Internationally, the concept of a conservative start of treatment and a subsequent change to broader spectrum therapy for non-responders has been challenged (113, 114). An alternative strategy involving initial broad spectrum therapy (carbapenems, cephalosporins, quinolones in monotherapy or in combination with others) and de-escalation (decreasing the number or the spectrum of the antibiotics, dose reduction, shorten the duration of treatment) accounting for the patient's clinical response and microbial testing, is gaining momentum. For serious infections in geographic locations with high level of resistance this strategy has proven successful in reducing mortality and length of hospitalization (115, 116). However, the long time consequences on emergence and spread of resistance are not well known (117).

Bacteria have developed a variety of mechanisms as protection against antibacterial agents, and some species have intrinsic resistance against single substances or classes of antibacterial agents (109). Bacteria acquire resistance either by spontaneous mutations or by horizontal gene transfer (conjugation, transformation or transduction), and the rate at which susceptible strains evolve or reacquire resistance decides the emergence of new resistant strains.

The mechanism by which antibacterial agents select for resistance depends on the species. Treatment of tuberculosis is long lasting and bacterial resistance may evolve in the host by mutation. Choosing a treatment strategy that prevents development of resistance in the treated patient will also reduce the risk of spreading resistant strains to the community. For most other important human pathogens, rapid resistance development in the treated patient is a rare event, and resistance is mediated mainly by shift in the population structure, or horizontal transfer of resistance traits from other bacterial populations (102). For example one study identified an increase in resistance in *Escherichia coli* against commonly prescribed antibacterial agents during treatment, but a decline to baseline levels in less than two weeks after cessation of therapy (118). For some pathogens the relative use of certain broad spectrum agents both at the

individual and at an aggregated level is positively associated with increased risk of infection with a resistant strains (111).

In pneumococci, oral penicillins promote resistance by increasing clearance of susceptible strains. In contrast, oral cephalosporins apparently increase the acquisition of new pneumococcal resistant strains during or shortly after treatment (119). Both mechanisms will contribute to the dissemination of resistant strains at the population level. Resistance in *Streptococcus* spp. against macrolides is acquired either via the *mef* gene, which encodes for an efflux pump mechanism, or via the *erm* genes which encode for modifications of the macrolide binding site at the bacterial ribosome (120). These mechanisms cause a high degree of resistance with erythromycin minimum inhibitory concentrations (MIC) of up to 512 mg/l. There are ecological data suggesting a link between consumption of antibacterial agents and resistance in *Streptococcus pneumoniae* (121, 122). High rates of resistance correlated to geographical areas with high consumption, and selective pressure on resistance expression via *mef* and *erm* genes has been documented for macrolides. A recent clinical trial with healthy volunteers assessed the effect of azithromycin and clarithromycin in promoting macrolide resistance in oral streptococci (123). Both treatments induced an increase in resistant pneumococci, and the increased level of resistance over the placebo group persisted for more than six months. Exposure to clarithromycin decreased the carriage of the *mef* gene and increased the carriage of the *erm* gene, and azithromycin doubled the MIC for erythromycin in streptococci that carried the *mef* gene.

Sub inhibitory concentrations of quinolones modulate the expression of resistance determinants, specific adhesins and other virulence associated determinants in methicillin resistant *Staphylococcus aureus* (MRSA) (124). The potential of a strain to cause epidemics depends on extraordinary virulence in combination with efficient colonization and host-to-host transmissibility. The virulence is associated with the severity of disease, while colonization capacity and transmissibility may explain the capability of spread and persistence. The underlying molecular factors for these phenotypes may be entirely different (125).

In summary, the level of bacterial resistance in human bacterial pathogens is positively associated with the selection pressure from different classes of antibacterial agents and the amount of consumption as a function of dose and time. Although the dynamics of the emergence of resistance is pathogen specific, it also depends on

different variables such as the biochemical mechanism conferring resistance, the genetic basis for the resistance, the antibacterial agent under consideration, bacterial mutation rates, mechanisms and frequencies of horizontal spread of resistance determinants between species and genera, shifts in bacterial population structures as a result of non-optimal treatment regimens, and the mechanisms of transmission and clonal spread of resistant strains as a function of lifestyle and culture (126). The transmission dynamics of resistant bacteria between outpatients are complex and incompletely understood, but involve numerous individual- and population-level factors (4, 127). Although the impact of the use of antibacterial agents for resistance emergence is undisputed, a precise quantification of the risk factors involved remains to be achieved (128).

4.5 Interventions to change suboptimal usage of antibacterial agents

There is a wide range of circumstances where consumption of antibacterial agents can be referred to as suboptimal. This includes misuse against infection of viral origin, excessive use of broad spectrum in stead of narrow spectrum antibacterial therapy, suboptimal dosage in relation to the pharmacodynamic- and the pharmacokinetic properties of the therapeutic agents, characteristics of the individual patient, untimely initiation of therapy, irrational choice of therapy in relation to the focus of the infection and knowledge of local ecology, and failure to initiating de-escalation in response to favorable microbial diagnostics or clinical response. Suboptimal consumption of antibacterial agents increases emergence of resistance, the risk of therapeutic failure and adverse reactions, and brings about unnecessary costs (75, 129-132).

When approaching the different aspects of suboptimal usage of antibacterial agents, interventions necessarily have to address a wide range of measures and take advantage of different designs. Numerous bodies have implemented a large number of interventions towards professionals or lay people using a variety of methods, alone or in concert, to improve suboptimal consumption of antibacterial agents both in the out-patient setting and in hospitals. Mostly, these programs have been implemented at the national or the local level, but there are also some examples of international initiatives from The World Health Organization and the European Union (133). Some programs have been running for more than a decade, and changes in the consumption of targeted antibacterial agents are well documented (134, 135).

Hospitals

Although the consumption of antibacterial agents in hospitals only accounts for a small part of the total consumption, suboptimal use in hospitals is increasingly recognized to have serious consequences not only for the patients, but also for the pattern of resistance in common human pathogens outside the hospital (100). Despite huge efforts in education, development and implementation of national guidelines and local formularies, recent studies still suggest a substantial amount of inappropriate prescribing (136). It is obviously challenging to change attitudes, expectations and behavior on treatment of infectious diseases because the determinative factors for change in prescription practice depend heavily on the clinical setting and the location (85). Thus, there is no single type of intervention that can be universally recommended (137).

Unfortunately, for a large proportion of the intervention initiatives, the true effects are poorly documented. This is mainly due to methodological flaws in the study design (96, 138), but there are also examples of studies with adequate design but with inappropriate choice of endpoints (96). Valid designs to study the effect of interventions are randomized clinical trials, controlled clinical trials, interrupted time series, time series, and controlled before and after studies.

Outcome of interventions

Most interventions aim to reduce the total consumption of antibacterial agents, to reduce the consumption of one or several broad spectrum agents, or to optimize the treatment regimens, but there are also a few examples of interventions that seek to increase the consumption of antibacterial agents (96, 138). The majority of the studies report outcomes on the consumption of the targeted agents, and some also report on clinical and microbiological outcomes. The results in the studies reporting clinical outcomes, mainly on mortality and readmission, are heterogeneous. In studies aiming to reduce the consumption of antibacterial agents, there are almost an even balance between studies reporting deterioration and improvement in clinical outcomes. The upper boundary of the confidence intervals suggests increased mortality risks (96). According to a recent Cochrane review, only a minority of the studies reporting effects on microbial outcomes provide convincing evidence that changes were caused by the intervention (29). This may in part be related to the method of how resistance is reported. Use of proportions of resistant isolates to assess the impact of the consumption of antibacterial agents instead of rates may be misleading, as proportions are dependent on both the susceptible and resistant bacterial populations while the incidence of resistance only depends on the resistant population (139). A French study that included data from 47 hospitals, found a stronger correlation between the consumption of antibacterial agents and the rate of MRSA and drug resistant *Pseudomonas aeruginosa* infections than between consumption and the proportion of resistance in these organisms (140). However, the cited Cochrane review only included studies published before 2004. Subsequent studies provide further evidence that reducing the consumption of quinolones and cephalosporins can reduce rates of MRSA and *Clostridium difficile* infections (95, 103, 141-145).

Interventions aiming to reduce the consumption of a single antibacterial substance or restricting the use of a drug class will result in a shift towards other treatment strategies, which subsequently may lead to emergence of other resistance patterns. Increasing incidence of extended spectrum beta-lactamases (ESBL's) in

Enterobacteriaceae following restrictions to the use of quinolones and replacement by cephalosporins or carbapenems have been highlighted by several authors, and restrictions to the use of cephalosporines have resulted in increased prevalence of carbapenem resistant *Pseudomonas aeruginosa* (144, 146, 147). However, a recent study covering 22 academic hospitals found that those hospitals restricting the use of carbapenems also used less quinolones than those with no restrictions. Restrictions in the use of carbapenemes were associated with lower incidence of resistance in *Pseudomonas aeruginosa* (148). Interestingly, these authors did not report on possible confounders such as infection control measures or the consumption of and resistance to cephalosporins. Information on concurrent switch of therapy to untargeted antibacterial agents is often scarce, and assessments of possible sustained effects on the pattern of resistance in common human pathogens after the termination of the projects are lacking.

Heterogeneous use of antibacterial agents slows the emergence of resistance, and withdrawal of a class of antibacterial agents theoretically limits the selective pressure from these agents. This is the underlying principle for the introduction of antibiotic cycling (AC) as an option to reduce the emergence of resistance. AC is a scheduled substitution of a class of antibacterial agents with a different class with a comparable spectrum of activity. This substitution may be followed by any number new substitutions, but the original class must be reintroduced in order to complete the cycle (149). However, mathematical modeling indicates that AC will be inferior to combination therapy, mainly because combination therapy gives greater heterogeneity at the scale relevant to bacterial populations (93, 150). The few studies assessing the effect of AC on bacterial resistance, and which are not seriously hampered by methodological flaws, are inconclusive (149).

Only a minority of the studies on interventions to promote prudent prescribing are multicenter studies. This raises concerns on the external validity of the studies. Furthermore, due to lack of standardization in design and choice of endpoints, it is difficult to perform a meta analysis on results from single hospital interventions (96).

Outpatient setting

Interventions to promote prudent prescribing of antibacterial agents in the out-patient setting have targeted inappropriate prescribing against viral infections, the choice of therapy and the interaction between the patient and the physician and physician and patient education (138). The intervention strategies can be categorized as physician

education alone, patient education alone, variants of physician and patient education combined, and physician and patient education with audit and feedback. Several studies have used strategies that target both patients and physicians. Valid study designs are considered to be the same as for interventions in hospitals (132). The majority of these studies address treatment of acute respiratory tract infections and report on outcomes on the rate of appropriate prescribing (proportion of patients receiving treatment, choice of therapy and length of treatment), the filling of delayed prescriptions, the incidence of colonization or infection with a resistant organism and the incidence of adverse effects (132, 138).

Outcome of interventions

A recent review identified 935 citations on interventions in ambulatory care of which 165 were reviewed and 43 subsequently included in the review. Only 30 of these presented data that allowed quantitative analysis, but due to flaws in the reporting of the data it was impossible to perform a meta-analysis. The authors concluded that no single intervention strategy or combinations of strategies are clearly superior, but interventions targeting specific conditions or patient groups tend to have less impact on total use of antibacterial agents than interventions targeting broader patient groups (132). There was no statistically significant effect between active and passive educational strategies towards physicians, but this may be a consequence of low statistical power due the low number of included trials (n=10) and the heterogeneity between the trials. The slightly higher effects from active interventions compared to passive dissemination of information, and from interventions using mass media are promising but warrant further investigation.

Another recent review on control strategies of the consumption of antibacterial agents in pediatric populations in hospitals and ambulatory care, included 28 studies of which six measured the impact of the intervention on microbial resistance (151). However, none of these six studies were performed in an ambulatory care setting. On the other hand, the lack of trials addressing this subject is not unexpected as mathematical modeling approaches suggest change in the consumption of antibacterial agents to have minimal immediate effect on rates of change of resistance (152).

5 Aims

The overall aim of the studies was to contribute to rational use of antibacterial agents.

Acute otitis media (AOM)

To contribute to prudent prescribing of antibacterial agents by examining whether educational efforts towards health care personnel and patients could reduce the proportion of patients with acute otitis media (AOM) receiving an antibiotic prescription, increase the relative use of penicillin V, and investigate to what extent the prescriptions against AOM were dispensed.

Enterococcal isolates, susceptibility and consumption of antibacterial agents

To contribute to optimal drug therapy of enterococcal infections by determining; i) the susceptibility of enterococcal species to commonly used antibacterial agents in a cross sectional collection of isolates from five Nordic hospitals, ii) to obtain information on the species distribution and population structure of resistance traits, iii) and by correlating enterococcal resistance to the usage of antibacterial agents in the same hospitals.

***Clostridium difficile* associated diarrhea (CDAD)**

To describe the incidence of *Clostridium difficile* associated diarrhea (CDAD) at two university hospitals (Aker and Tromsø), and to investigate a possible association between CDAD and different hospital usage of broad spectrum antibacterial agents.

Pharmacokinetics of netilmicin in neonates

To contribute to optimal netilmicin treatment in neonates by validating a new simplified high-dosage, extended-interval dosing regimen.

6 Methods

Paper I

We used a controlled before-and-after design to assess the impact of implementing national guidelines in combination with educational efforts towards health care personnel and parents on treatment of acute otitis media (AOM). The Emergency Call Service (ECS) in Tromsø was the intervention site, and the ECS in Harstad was the control site.

Patients aged 1 to 15 years diagnosed with AOM were eligible for intervention. The criteria for the clinical diagnosis of AOM were acute ear-related symptoms (fever, otalgia, irritability) and signs of middle ear fluid (MEF), redness and bulging of the tympanic membrane, or perforation of the tympanic membrane and discharge of MEF. The baseline period was December 1997 to the end of March 1998, and the intervention period was December 1998 to the end of March 1999.

We extracted relevant patient data, information on diagnosis, and choice of therapy with specially designed software from the patient administrative system at both sites. All data were encrypted using the MD 5 algorithm. Relevant dispensing data from the pharmacies in Tromsø were extracted and encrypted with the same algorithm.

Categorical data were tested using the chi-squared (χ^2) test. All tests were 2-sided, and $p \leq 0,05$ was considered significant.

Paper II

We collected Enterococcal strains and consumption data on antibacterial agents from five tertiary care university hospitals in Denmark, Iceland, Norway and Sweden. Three groups of strains were included; i) all blood culture isolates from 1999; ii) consecutive clinically significant isolates from in-patients; iii) consecutive clinically significant isolates from outpatients. Groups ii) and iii) were collected over a 3-month period and contained maximum 40 strains from each hospital, and only the first isolate per patient was included.

After speciation, all strains were screened for resistance to ampicillin, gentamicin and vancomycin by inoculation on specific agar plates. Isolates growing on any of the agar

media were further tested by E-test for the respective antibacterial agent, and the results were categorized according to NCCLS for susceptibility. Intermediately susceptible or resistant strains to vancomycin or teicoplanin were analyzed with PCR for *vanA*, *vanB* and *vanC* genes, and 13 *E. faecium* strains with reduced susceptibility to ampicillin were examined by pulse-field gel electrophoresis (PFGE) of *SmaI* chromosomal digests. We compared banding patterns visually and by the GelCompare® software package.

National data on consumption of antibacterial agents were given as mean number of DDD/1000 inhabitants/day for the years 1997-99. Hospital consumption data were given as mean number of DDD/1000 bed days/year and as a mean proportion of total use in DDD for the years 1997-99. Hospital consumption data were based on sales from the respective hospital pharmacies. We used the 1999 version of the ATC system and DDDs, and all hospital data were aggregated to ATC main groups on the third or the fourth level.

Paper III

We collected information on local guidelines for treatment of infectious diseases, educational efforts and consultation visits during implementation of the guidelines, the consumption of antibacterial agents, the total number of and the proportion of positive *C. difficile* tests, the number of patients with antibiotic associated diarrhea (AAD) at four different points in time, bed occupancy rates, average length of stay, isolation rooms and other facilities for infection control, at two tertiary care university hospitals in Norway. All data concerned the year 2001.

Hospital consumption data were based on sales from the respective hospital pharmacies, and were given as number of DDD/1000 bed days/year. Information on *C. difficile* tests was extracted from files at the respective microbial laboratories. Four point prevalence studies gave data on the proportion of patient receiving antibiotics, indication for treatment and the proportion of these patients with AAD. The Norwegian Research Unit provided data on bed occupancy for Hospitals (SINTEF-UNIMED) and average length of stay from the respective hospitals. The infection control nurses recorded relevant infection control facilities.

Categorical data were tested using the chi-squared (χ^2) test. All tests were 2-sided, and $p \leq 0,05$ was considered significant.

Paper IV

We undertook an open, prospective non-comparative study in the neonatal intensive care unit at a tertiary care university hospital. All infants (n=129) less than 3 months without severe perinatal asphyxia, renal anomalies or known renal impairment and who received at least 3 doses of netilmicin were eligible over a period of 26 months from September 2000.

Data collected included gestational age (GA), postnatal age (PA), postmenstrual age (PMA) (GA+PA), birth weight, complete blood count, blood cultures, C-reactive protein (CRP), and plasma creatinin (7,5 hours after the completion of the third dose). Susceptibility testing of invasive isolates was performed with the paper disc method and MIC for netilmicin was determined with E-test.

Netilmicin 6 mg/kg was administered as an i.v. infusion over 30 min, and dosing intervals were set at 24 or 36 hours depending on GA, PA and PMA. All patients received ampicillin or cloxacillin in addition to netilmicin. Sample for through serum netilmicin concentration (SNC) was drawn just before the third dose (at 48 or 72 h). In addition, sample for SNC was drawn 0,5 h and 7,5 hours after the infusion of the third dose. The SNC was determined with a standard fluorescence polarization immunoassay.

We calculated the elimination rate constant using a one-compartment first order model. Baseline data were given as mean values with standard deviation. Group differences were presented as mean values with standard error of the means. The Mann-Whitney U-test was used for intergroup comparisons, and a linear regression model was used to correlate $t_{1/2}$ and GA. $p \leq 0,05$ was considered significant.

7 Summary of papers and main results

Paper I

Småbrekke L, Berild D, Giæver A, Myrbakk T, Fuskevåg A, Ericson JU, Flægstad T, Olsvik Ø, Ringertz SH. Educational Intervention for Parents and Healthcare providers Leads to Reduced Antibiotic Use in Otitis Media. *Scand J Infect Dis* 2002; 34(9): 657-9.

The proportion of patients at the ECS in Tromsø receiving a prescription of antibiotics was reduced from 90% to 74%, and the proportion of prescriptions on penicillin V was increased from 72% to 85%. There were no statistically significant changes at the control site. There was no significant change in the age distribution of the patients diagnosed with AOM either in Tromsø or Harstad, but the age distribution of the patients receiving a prescription of antibiotics changed significantly in Tromsø in the study period. After intervention, a lower proportion of the two youngest age groups and a higher proportion of the oldest age group received a prescription. There was no change in Harstad. During the intervention there was a reduction in the proportion of patients diagnosed with AOM at the ECS in Tromsø, and no significant change in Harstad. The proportion of dispensed prescriptions was 70% both in the baseline and the study period.

In conclusion, we found a reduced total consumption of antibiotics and a diminished use of broad-spectrum antibiotics for AOM in children aged 1 to 15 years attending emergency call service in Tromsø. Extraction of data on antibiotic use for AOM based on prescriptions only will overestimate the actual use of antibiotics in this age group.

Paper II

Simonsen GS, Småbrekke L, Monnet DL, Sørensen TL, Møller JK, Kristinsson KG, Lagerqvist-Widt A, Torell E, Digranes A, Harthug S, Sundsfjord A. Prevalence of resistance to ampicillin, gentamicin and vancomycin in *Enterococcus faecalis* and *Eterococcus faecium* from clinical specimens and use of antimicrobials in five Nordic hospitals. J Antimicrob Chemother 2003; 51(2): 323-31.

A total of 509 isolates were included in the study; 420 *E. faecalis*, 82 *E. faecium*, four *E. gallinarum*, two *E. casseliflavus* and one *E. hirae*. Among 156 blood culture isolates there were 104 *E. faecalis*, 49 *E. faecium*, two *E. gallinarum* and one *E. casseliflavus*. From the consecutive non-systemic isolates from in- and outpatients, 84,2% and 95,3% were *E. faecalis*, respectively. The overall proportion of *E. faecium* from inpatients was 22,1%, and 4,1% from outpatients. *E. faecium* was more prevalent in blood culture (31,4%) than from non-systemic (14,1%) inpatient isolates.

We did not find reduced susceptibility to ampicillin in *E. faecalis*, whereas resistance in isolates of *E. faecium* differed from 33,3% to 61,3% between hospitals. There was no difference between high level gentamicin resistance (HLGR) in *E. faecalis* isolates of in- and outpatients in either hospital, but HLGR prevalence was significantly higher in Bergen and Uppsala. HLGR in *E. faecium* was only detected in one hospital. PFGE typing of these strains showed two groups of four isolates with more than 80% identity.

The mean yearly national consumption varied between 13,5 and 21,3 DDD/1000 inhabitants/d in Denmark and Iceland, respectively, and there were large differences in yearly consumption of extended spectrum penicillins, glycopeptides and aminoglycosides. In the participating hospitals, the mean consumption of antimicrobials varied between 295 and 483 DDD/1000 bed-days/year, and there were large differences in the consumption of extended spectrum penicillins, cephalosporins, glycopeptides and aminoglycosides.

The study confirmed a high proportion of *E. faecium* among hospital enterococcal isolates with an average of 31,4% in blood cultures and 14,1% in the non-systemic isolates. The data indicated an overall low prevalence of resistance. All *E. faecalis* isolates were susceptible to ampicillin, but we found large differences of HLGR between hospitals, although Nordic countries generally report low prevalence in

enterococci. Almost half of the *E. faecium* isolates were resistant to ampicillin and aminoglycosides. There was a cluster of HLGR isolates from one hospital, and many of these isolates were also resistant to gentamicin. Some of the isolates were clonal.

There was a factor of 1,6 in difference in overall use between the hospital with the lowest and the highest consumption, and there was also a difference in the pattern of antimicrobial agents being used. Although the cluster of ampicillin resistant/HLGR *E. faecium* was found in the hospital with the highest consumption of extended spectrum penicillins and aminoglycosides, this was not sufficient to establish a causal relationship. The study did not contain sufficient data for analysis of the dynamic relationship between antimicrobial use and occurrence of resistant bacteria.

In conclusion, the study documented low use of antibacterial agents and low level of resistance in *E. faecalis* and *E. faecium* in Norway compared to other regions of Europe and the USA. The large differences between hospitals in the amount of use, choice of therapy, and in the prevalence of resistance, indicated a potential for further improvement of antibiotic policies and infection control.

Paper III

Berild D, Småbrekke L, Halvorsen DS, Lelek M, Stahlsberg EM, Ringertz SH. *Clostridium difficile* infections related to antibiotic use and infection control facilities in two university hospitals. J Hosp Infect 2003; 54: 202-6.

Total consumption of antibiotics was on the same level for both hospitals (47 – 60 DDD/100 hospital days/year), but the pattern of use was different. The use of broad spectrum penicillins was threefold higher at Aker, while especially the use of cephalosporins, clindamycin and carbapenems was higher in Tromsø. Despite the reduction in use of broad spectrum antibiotics at Aker, the incidence of CDAD increased and was higher than in Tromsø until 2001. There was no significant change in diagnostic policies for CDAD in either hospital. Data from the point prevalence studies showed no difference between the hospitals in the proportion of patients receiving antibiotics, or in the proportion of patient with AAD. Single rooms, isolation rooms and other facilities for infection control were more available in Tromsø, but the bed occupancy rate was higher and the duration of hospital stay was longer at Aker.

The results indicated that the incidence of CDAD depended not only on amount and pattern of antibiotic use, but also on infection control facilities and clinical factors. Our data were insufficient to determine the impact from the specific factors on the incidence of CDAC.

Paper IV

Klingenberg C, Småbrekke L, Lier T, Flægstad T. Validation of a simplified netilmicin dosage regimen in infants. *Scand J Infect Dis* 2004; 36(6-7): 474-9.

Aminoglycosides exhibit concentration dependent bactericidal and postantibiotic effects. High peak concentrations, at least 8 to 10 times the minimal inhibitory concentration (MIC), are associated with improved therapeutic outcome in life-threatening bacterial infections in adults. Plasma concentrations above 2 mg/L shortly before the next dose are associated with increased risk of oto- and nephrotoxicity.

In 110 infants, during first week of life (mean gestational age (GA) 35,5 – range 24 to 42 weeks), the mean plasma concentration 30 minutes (C_p 0,5 h) after completing the infusion was 10,5 mg/l. The mean C_p 0,5 h was significantly lower (9,0 mg/l) in 38 infants with post natal age over 7 days. Fourteen of 15 infants with $C_{p_{min}} > 2$ mg/l had GA <28 weeks. During the first week of life, we found significant correlations between GA and elimination half-life of netilmicin, and between plasma creatinine and elevated $C_{p_{min}}$. There was no correlation between C_p 0,5 h and GA.

This dosing regimen yielded C_p 0,5 h above 8 mg/L in 88 % of all treatment courses. In the first week of life, a dosing interval of 48 h for infants of GA <29 weeks, 36 h for infants of GA 29 to 36 weeks and 24 h for full term babies seem appropriate to avoid the majority of elevated $C_{p_{min}}$ levels and still obtain adequate therapeutic effects.

8 Discussion

Immediate initiation of an effective drug treatment against the causative agent(s) in a serious bacterial infection is associated with a favorable outcome for the patient and reduced treatment costs. However, this approach must be balanced against possible adverse drug reactions and unfavorable ecological effects. The widespread and unnecessary use of broad spectrum antibacterial agents exerts a continuous selective pressure on bacteria and accelerates the emergence and spread of resistance. The substantial consumption of antibacterial agents due to inappropriate treatment against self limiting infections contributes to the unnecessary emergence and persistence of resistant pathogens (114).

8.1 Acute otitis media

Well designed clinical trials over the last two decades have shown only moderate effects of antibacterial therapy against uncomplicated AOM for children older than 6-12 months (153). It is increasingly recognized that antibiotic treatment is not necessary for all cases of AOM. However, internationally there are still clinical guidelines advocating liberal use of antibiotics on this indication, and clinical practice is highly inconsistent and frequently non-compliant to restrictive guidelines (154). It is highly questionable whether further research should aim to elaborate possible minor benefits from antibacterial treatment on this indication. A better theoretical understanding on how to optimize organizational settings, provider and patient behaviors and patient expectation in connection to this indication would be valuable (155). Furthermore, there are undoubtedly some patients benefitting from treatment, and measures to better identify this cohort are required.

The extent of treatment and choice of therapy

Pre-intervention, approximately 90% of those diagnosed with AOM at the ECS in Tromsø received treatment with antibacterial agents (156). This is around 20 percentage points higher than was found in a study from general practice in southern Norway (157). Our data does not explain this difference, but they probably reflect different patient populations and a more liberal treatment strategy because follow up of the patients are more challenging in the ECS setting. During the intervention, 74% of the AOM patients at the ECS in Tromsø received a prescription on antibacterial treatment, but only 70% of the prescriptions were dispensed at the pharmacy. The proportion of dispensed prescriptions was the same in the baseline and the study periods. We are not aware of other studies providing information to which extent the

prescriptions on AOM are dispensed. Our data suggest that approximately 50% of the patients during the intervention period received treatment, a proportion which still is considerable higher than for example in the Netherlands.

Interestingly, epidemiological data document lower incidence of mastoiditis, a serious complication to AOM, in the USA compared to the Netherlands and the Scandinavian countries (158). Considering that more than 95% of children below 15 years receive antibiotics against AOM in the USA, a rate reduction of mastoiditis of approximately 2/100 000 persons/year has to be weighted against increased risk of adverse reactions and emergence of bacterial resistance. A recent study from Iceland found increased incidence of mastoiditis in children under 18 years in a period when the consumption of antibacterial agents was reduced (159). The incidence in the adult population was unchanged. Among the children with mastoiditis, 80% had been diagnosed with AOM, and 72% of these patients had received antibacterial treatment. However, the authors used sales figures of fluid antibacterial agents as an approximation for the consumption of antibacterial agents in this cohort. The validity of this approximation was not assessed, but the long period of observation is to some extent reassuring. In summary, the above discussion provides no proof of causality between a high rate of antibiotic treatment and a reduced risk of mastoiditis, but highlights that intervention studies may lack the statistical power to identify infrequent adverse complications and calls for continuous assessment of the incidence of mastoiditis.

Our data suggest good compliance to Norwegian guidelines on choice of therapy. We found that 85% of the AOM patients during the intervention period received a prescription on phenoxymethylpenicillin (PenV). This observation apparently contrasts the study by Straand et al, in which 58% of patients with ear infections received PenV, but the study by Straand covered all age groups. In addition, “ear infections” also covers external otitis where the choice of therapy is different.

In a recent Swedish study, 192 children aged 2 to 16 years with symptoms of AOM lasting less than four days and with no perforation, were randomized to treatment with PenV or no treatment with antibacterial agents (160). The median recovery time was 4 days in each group, but the group receiving PenV used significantly less analgesics. There were no differences in the proportion of patients with middle ear effusions or perforations at the final control after three months. These results need to be confirmed, but they suggest a limited effect of PenV in certain patient populations. A recent meta-

analysis found a statistically significant effect on persistence of symptoms after 2 to 4 days from antibiotic treatment of AOM, but questioned the clinical relevance of the small incremental effect seen, considering the increased risk for adverse outcomes (153). The authors also highlight the possible public health benefit from limiting antibiotic use against AOM, and the increased individual risk for colonization with resistant strains.

Interventions – methodological challenges

Numerous intervention studies covering major disciplines in health care have been published, but there is still a lack of evidence to support decisions about which designs and strategies are likely to be optimal in the presence of various implementation barriers under different circumstances. No relationship was found between the number of components and the effects of multifaceted interventions or the type of intervention, but some data indicate better effect in settings where the potential for improvement is high (132, 155).

Flaws in the design of the intervention can hamper the possibility to accurately estimate the efficiency of guideline dissemination and the implementation strategies. Uncontrolled trials, before and after studies, and time series with few pre-intervention data points are prone to bias and confounding. Secular trends, cyclical patterns like seasonal trends, random fluctuations with no discernible pattern, short time interventions and autocorrelation are serious threats to correct estimates of intervention effect (96, 132, 155). Controlled before and after studies suffer additional threats from the Hawthorne effect and contamination. The Hawthorne effect is a phenomenon that occurs when individuals alter their performance or behavior due to the awareness that they are being studied or observed (161). The change may be positive or negative depending on the situation. A special variant of the Hawthorne effect occurs when the members of the control group alter their behavior when they realize they are in the control group.

Contamination occurs when ingredients in active interventions are transportable and difficult to confine. This imposes a risk for dissemination of elements of the intervention to the non-intervention site, resulting in bias, reduced power and an underestimation of the magnitude of effect. The risk of contamination increases when the intervention is aimed at professionals, if the intervention is desirable, and if there is some kind of interaction between subjects in the two groups. Contamination and its

effects have only been quantified in a few studies using a randomized controlled design (155).

Some of the methodological challenges concerning the evaluation of the effect of interventions can be overcome by adequate design. If the effect of an intervention is investigated in only two study sites, the use of interrupted time series (ITS) will probably increase the validity of the results. In ITS data are collected at several time points before and after the intervention. This protects against artifacts due to secular- or seasonal trends, and is also informative on the sustainability of the intervention. If several study sites are analyzed, randomized controlled trials (RCT) should be considered as this design gives the strongest possible protection against bias and confounding.

Interventions - national campaigns

There are examples of national campaigns addressing prudent use of antibacterial agents from several European countries, the USA, Canada, several Asian countries and Australia (133, 162, 163). These campaigns have been multifaceted including regulatory measurements like drug licensing, drug access and reimbursement in combination with intervention towards health care professionals and consumers. Initiatives towards health care professionals have focused on improved diagnosis through use of rapid diagnostic tests, guidelines on prudent prescribing, practice profiling and feedback, educational programs and use of delayed prescriptions. Consumer interventions have been educational in nature, and the most successful initiatives have taken advantage of broad programs including television advertising, printed matter, presentations in schools and day-care centers, and information sharing on web-sites (126). However, there are insufficient data on the absolute effects and the sustainability of the different types of interventions available (132, 138). Further studies are also warranted to establish the optimal balance in interventions between education and empowerment versus restriction, and how to take maximum advantage of media activity.

Interventions - local initiatives in the outpatient setting

Interventions in the out-patient setting have addressed inappropriate use of antibacterial agents for viral infections, choice of therapy for various indications, and the duration of treatment for respiratory tract infections (138). Didactic lectures, printed educational materials for health care personnel or audit and feedback alone usually have produced none or only modest effects on prescribing. Delayed

prescriptions for self-limiting infections or for infections which immediate treatment may be postponed, have reduced the consumption of bacterial agents apparently without increasing morbidity. Educational strategies addressing physicians, patients and the public through various channels have successfully reduced prescribing of antibacterial agents on inappropriate indications (138), and change in reimbursement has changed the choice of therapy for respiratory tract infections (43, 164, 165). There are only a few examples of studies on the effects of interventions on bacterial resistance, and studies with adequate control for bias and confounding are scarce. A Cochrane review identified four studies with sound methodology. Only one study from Finland documented a sustained reduction in the level of resistance group A streptococci in association with the intervention (166).

Intervention at the Emergency Call Service (ECS) in Tromsø

A previous study documented a high turnover of children with acute otitis media (AOM) during the winter months, and high rates of antibiotic treatment of AOM combined with a low rate of treatment with narrow spectrum penicillin at the ECS in Tromsø (156). On this basis, we judged the ECS in Tromsø to be a relevant location for an intervention aiming to implement national guidelines on treatment of AOM.

There was a discrepancy between an ideal design for the intervention, and what was possible to carry through at the study site. We were, for example, unable to hire extra personnel that would have enabled us to follow up patients who refrained from a visit to the doctor after receiving the folder which described information on symptomatic treatment. Such information would have been valuable to determine to what degree these patients postponed their consultation at the ECS for a later consultation by the family doctor. Data were also insufficient for a satisfactory cost evaluation, not only concerning the costs for planning and implementation of the intervention, but also for possible costs from changes in clinical practice.

There were no data available on local or national incidence of AOM in the baseline period or in the study period. It is well documented that the incidence of some infectious diseases changes over time, but how this affects the total consumption of antibacterial agents is not straight forward because diagnostic routines, treatment strategy, and the proportion of patients receiving treatment may change over time (167).

Data from USA over the period 1996 to 2005 give conflicting numbers on the proportion of children with AOM receiving treatment with antibacterial agents. One

study using retrospective data from emergency departments found an increase in the proportion of children up to 12 years receiving treatment (168). Another study focusing on children younger than two years enrolled in private insurance plans covered more than 40 000 persons yearly during the period from 1997 to 2004. Using the period from 1997 to 1999 as baseline, the investigators found a 43% decrease in the rate of visits due to AOM, and a 42% decrease in the rate of prescriptions in 2004 (169). Similar results were found in another study addressing the change in the rate of antibiotic prescribing in children younger than 18 years. The investigators studied the claims for dispensed medications and physician visits in 9 health plans in the USA from 1996 to 2000 (170), and found that reduction in rate of antibiotic prescribing differed over age groups, but was on average approximately 25%. A concurrent reduction in the rate of diagnosis of AOM accounted for half of this reduction, and the investigators speculate that public campaigns and media attention has contributed to changes in diagnostic thresholds for possible viral infections.

A similar trend was found in the UK (171). In a retrospective study on data from 108 general practices covering on average a population of approximately 642 700 persons between 1994 to 2000, the investigators found that the standardized consultation rate for respiratory tract infections (RTI) fell by 35% to 273 per 1000 registered patients per year. The proportion of consultations where patients received a prescription for an antibacterial agent fell from 79% to 67%. The authors concluded that the reduction in prescribing against respiratory tract infections was a result of fewer persons visiting the general practitioner for such infections, and a lower proportion of those diagnosed with RTI receiving treatment with antibacterial agents.

In a recent study from Kalmar County in the south-east part of Sweden, the investigators followed all patients (n=146454) attending 23 of the 32 health care centers in the county from June 1999 to the end of 2005 (59). During this period, RTI's were diagnosed in 240 447 consultations. There was a significant reduction in the number of consultations for AOM, acute tonsillitis, laryngitis, and pharyngitis, but the proportion of patients receiving a prescription (44% to 46%) for an antibacterial agent was constant. The reduction was most evident for AOM and acute tonsillitis. There was no change in the rate of consultations for common cold, acute sinusitis, influenza and lower respiratory tract infections. New national guidelines in Sweden for the treatment for AOM and sore throat were launched in year 2000 and 2001, respectively. However, the investigators found no change in choice of the treatment for AOM until the season 2003 - 2004. The change in the treatment for AOM

coincided with a randomized controlled trial on the treatment for AOM in Kalmar County. It is unclear whether the change came as a result of a late implementation of the national guidelines or in connection to an information program launched as a part of the randomized trial.

Similar observations are made for other infectious diseases. Assessing national trends in ambulatory visits for skin and soft tissue infections in the USA, the investigators found a 50% increase in the rate of visits from 1997 to 2004 (172). Prescriptions recommended for community acquired MRSA infection increased 4-fold in the same period. Another research group also published similar results although that study only included patients who attended emergency departments in hospitals (173).

Due to the controlled before and after design, our intervention study is therefore prone to secular trends on the incidence of AOM or other forms of bias introducing systematic changes in the attendance of patients to the ECS, changes in diagnostic practice, or choice of therapy. The risk for bias could have been reduced by including data from at least three pre-intervention points, preferably from the same winter periods over the three previous years. We cannot rule out that Hawthorne effects or contamination have contributed to the results in our study. Hawthorne effects would increase the apparent effect of the intervention, while contamination would drive the results toward the null.

8.2 Enterococcal resistance to ampicillin, gentamicin and vancomycin and use of antimicrobials in five Nordic hospitals

The selection pressure from antibacterial agents at the hospital can be seen as a combination of the total amount of use within a hospital or a department over a time period, the profile and characteristics of the antibacterials used, the proportion of patients receiving treatment, and the number of treated patients. Obviously, there is no single variable that can capture all necessary information to accurately describe all aspects of drug usage.

Our study included 509 enterococcal isolates from five Nordic tertiary care university hospitals, and yearly national and hospital specific data on consumption of antibacterial agents. The number of isolates was limited, and the results should be interpreted with caution. However, the prevalence of resistance against ampicillin and gentamicin varied between the five hospitals, highlighting the need for local

surveillance. Due to the cross-sectional design, our study could not give information on the incidence of enterococcal infections, but documented the distribution of enterococcal species in three different groups of isolates.

The high proportion of *E. faecium* in hospital blood stream isolates is in accordance with other studies. Longitudinal data indicate an increasing incidence of enterococcal infections in tertiary care teaching hospitals, and an increasing incidence of infections with *E. faecium* (174, 175). This is worrisome, because a high proportion of *E. faecium* strains are resistant to ampicillin, and more than half of the strains resistant to ampicillin are also resistant to gentamicin. Empiric therapy for an enterococcal infection with ampicillin and gentamicin will thus carry a high risk for therapeutic failure. In addition to clonal spread of resistant strains, there is possibly also an association between the increasing incidence of *E. faecium* blood stream infections and an increasing consumption of broad spectrum antibacterial agents, changes in the hospital patient populations, or changes in the hygienic measures.

Data on hospital consumption of antibacterial agents at the five hospitals were given by the respective hospital pharmacies as mean over three years and adjusted to hospital bed days. This is a crude measure, and unsuitable for capturing short time variations in consumption and possible temporal relationships to the incidence of resistant strains. No data on consumption of antibacterial agents at patient level were available.

A parallel analysis of individual and aggregated data on exposure for antibacterial agents and resistance in Gram-negative bacilli found divergent results (23). The authors observed a minimal change in bacterial resistance at hospital level despite substantial increase in the consumption of third generation cephalosporins, quinolones, ampicillin-sulbactam, or decrease in the consumption of imipenem. At individual level, consumption of cephalosporins, quinolones, ampicillin-sulbactam, or imipenem was a significant risk factor for resistance. However, the effect of exposure at an individual level may also wane as a result of an interaction between an individual and a group effect (23).

Alternatively, it is possible to adjust the consumption of antibacterial agents to the number of new patients to the hospital. Several investigations on the linkage between the consumption of antimicrobials and resistance have adjusted to bed days, but it is unknown which denominator will give the best prediction of this relationship (23). This is probably of no importance in our study, but should be investigated in further

studies on models describing the temporal relationship between consumption of antimicrobial agents and resistance. For some antibacterial agents, DOT may be an alternative to DDD, but a serious limitation is that DOT does not distinguish between a low or high daily prescribed dose (16, 176).

The association between antibacterial consumption and resistance

In Norway, transferable vancomycin resistance is so far not established in clinical enterococcal isolates (15). This contrasts the situation in other parts of Europe and the USA and in other parts of the world where vancomycin resistant enterococci (VRE) have become endemic in hospitals. The nosocomial epidemiology of vancomycin resistant enterococci (VRE) has been extensively studied. However, to what extent the consumption of different broad spectrum- and anaerobic antibacterial agents increase the risk of colonization or infection with VRE remains unclear (177, 178). The emergence and spread of VRE in hospitals depends on several mechanisms including the exposure to antibacterial agents and to VRE reservoirs, and host factors related to colonization and infection. Although the exposure to different classes of antibacterial agents has been addressed in several studies, there have been controversies on which and to what extent different agents contribute to the emergence and spread of VRE (178). There have also been conflicting data between individual level studies and population level studies, possibly due to methodological flaws.

The epidemiology of enterococci in hospitals is complex, and the methodological approach to investigate the relationship between exposure to antibacterial agents and the proportion of VRE must take into account interactions between different antibacterial agents, dosage, the temporal relationship between consumption and the emergence of resistance, and the fact that the observations of resistance and consumption are dependent. In a study from Greece using time series and transfer function models, the investigators found that the bimonthly incidence of VRE per 1000 patient days could be predicted by the incidence of VRE the two previous months, and the consumption of extended spectrum cephalosporins, quinolones, glycopeptides and beta-lactam-beta-lactamase inhibitors. There was a positive correlation between the incidence of VRE and the consumption of cephalosporins, quinolones, and glycopeptides with a delay of two, two, and four months respectively, and a negative correlation with the consumption of beta-lactam-beta-lactamase inhibitors (178).

Interestingly, restrictive interventions on the consumption of glycopeptides and broad spectrum cephalosporins, at the population level, have not uniformly contributed to limit the emergence and spread of VRE, and the sustainability of successful interventions is poorly documented (177, 179). None of the previous studies referred to are randomized controlled trials (RCT), but on the other hand, RCT are probably not a suitable design to answer the question on possible association between the consumption of an antibacterial agent and the emergence of a specific resistance mechanism. Several of the studies carry a substantial risk for bias due to a before and after design with the control group from the same hospital. In addition, there is apparently no consensus on the definition of outbreaks versus endemicity that further increases the risk of time effects. Possibly, a comprehensive review of restrictive interventions also carries a high risk for publication bias (177). Further elucidation of a possible causal association between consumption of different classes of antibacterial agents and emerging resistance in *Enterococcus* spp. should be addressed in prospective multi-centre studies taking advantage of longitudinal data on resistance, consumption of antibacterial agents and analyze data using time series and transfer function modeling. Other variables like hygienic measures, length of stay, underlying diseases and the prevalence of resistance amongst out-patients should be accounted for as the emergence of resistance rarely is mono-specific (179). In addition, possible contribution from factors like the rate of re-acquisition, reduced fitness costs for strains carrying resistance determinants, directional selection of genetically linked traits and the stability of extra chromosomal elements carrying resistance determinants should be accounted for (5).

The association between consumption of antibacterial agents and resistance in other bacterial pathogens

There is a salutary theoretical foundation for a correlation between increase in use of antibacterial agents and the subsequent increase in the prevalence of resistant bacteria. Correspondingly, there is a theoretical framework supporting the assumption that a reduction in consumption of antibacterial agents should reduce resistance, but data from observational studies using ecological data on regional or national level are conflicting. Some studies investigating exposure to beta-lactams or macrolides and the risk of colonization or infection with resistant *Streptococcus pneumoniae* or *Streptococcus pyogenes*, have shown geographical correlations and quantitative relationships between consumption of beta-lactams, macrolides and resistance (56, 166, 180-182). Data from the United Kingdom (UK) and Northern Ireland showed an increasing trend in penicillin resistance in pneumococci up to 1997, but a decreasing

trend from 1999. UK pharmacy sales of oral macrolides and beta-lactams fell by approximately 30% in the late 1990s following a growing concern on problems with resistant strains. The fall in sales of macrolides was not associated with any decline in macrolide resistance (181).

An ecological study using national data on consumption and national surveillance data from published studies covering 20 European countries, found strong correlation between streptococcal resistance and antibacterial selection pressure from penicillins and macrolides on national level (183). A study from USA found that variations in resistance of *S. pneumoniae* were better explained by geographic variations in consumption of antibacterial agents than by spread of clones with certain serotypes. This was reflected by differences in the proportions of resistance within a particular serotype, rather than by the differences in the frequencies between serotypes harboring resistance (184).

Other investigators have been unable to show an impact on resistance of pneumococci or carriage of resistant pneumococci following a decline in the consumption of macrolides and beta-lactams (129, 134, 185). A study on sulphonamide resistant *E. coli* showed a 6% increase in the proportion of resistant strains following a 98% reduction in the use of sulphonamides over a period of 8 years (186). Five years later, a follow up study found sulphonamide resistance to persist undiminished (187). These contrasting observations suggest that other factors than antibacterial drug consumption is important contributors to preserve the level of resistance.

Applying time series and transfer functions to study the correlation between ceftazidime consumption and the percentage of resistant or intermediately susceptible Gram-negative bacilli, the investigators found the percentage of resistance to be a function of the percentage of resistance three and five months before, and the hospital ceftazidime use the previous month (188). Applying the same methods, the same investigators found similar correlations between imipenem usage and the percentage of resistant or intermediately susceptible *P. aeruginosa* strains.

Analyzing the dynamic relationship between monthly percentage of MRSA and hospital use of several antibacterial agents, a time series model including previous monthly percentage of MRSA, and consumption of macrolides, third-generation cephalosporins and quinolones as independent variables explained more than 90% of the monthly variation in prevalence of MRSA (103). An alternative model excluding

the monthly consumption of antibacterial agents explained approximately 81% of the monthly variation in the prevalence of MRSA.

Using a multiple linear regression model, no correlation was found between the percentage of resistance in Gram-negative bacilli and gentamicin consumption the same year (189). Changing the model and using the gentamicin consumption data from the previous year gave a significant correlation to the percentage of resistance. Other researchers have built linear regression models including the consumption of several antimicrobial agents and in addition defining a coupling fraction which describes the percentage of isolates resistant to an antibacterial agent that is also resistant to another agent (190). These models relying on several antimicrobial agents gave better correlation between consumption and percentage of resistance than models only taking one antimicrobial agent into account (191).

In summary, we documented the distribution of enterococcal species in three different groups of isolates. The high proportion of *E. faecium* in blood stream isolates is in concordance with other studies. Between the five hospitals, the consumption of antibacterial agents expressed as DDD/1000 bed days/year varied by a factor of 1,6, and we also documented diverging prevalence of enterococcal resistance against ampicillin and gentamicin between the hospitals. Our data were insufficient to establish a causal relationship between consumption and resistance, but highlighted the need for local surveillance.

Other considerations

The Antibiotic Centre for Primary Care (Antibiotikasenteret for primærmedisin) was established in Norway in 2006 as publicly financed project. The main tasks for the Centre are to initiate and support relevant research in primary health care, to develop guidelines and post graduate courses for physicians in primary health care and to develop relevant public information on the use of antibiotics (192).

There is yet no analogous body to address similar issues in hospital health care. However, a document on national strategies suggests to clarify the need for a centre covering hospital and other institutional health care (193). The establishment of a national body covering these tasks is highly desirable considering that hospitals are important locations for emergence and spread of resistant bacterial strains. In addition there is a lack of clinical trials addressing the treatment of important infectious diseases accounting for the low level of resistance in Scandinavia and the Netherlands

compared to most other parts of the world. Possibly, a national body could contribute to the initiation and support of this type of public health research.

All Norwegian hospitals are required to establish guidelines on treatment of infectious diseases (194). To my knowledge there has been no systematic evaluation on quality and implementation of local guidelines, nor has there been a critical appraisal of all costs involved. It is also highly questionable whether there is a need for local guidelines in hospitals in Norway considering that there are no major regional differences in the pattern of resistance amongst common human pathogens. Possibly, there should be more focus on implementation and compliance to national guidelines, and on coordination of multi-centre research to answer important clinical questions.

8.3 *Clostridium difficile* associated diarrhea in two university hospitals

Prudent prescribing of antibacterial agents to hospital inpatients reduces the cost of therapy, the risk of emerging bacterial resistance, and the risk of adverse side effects including the risk for *Clostridium difficile* associated diarrhea (CDAD) (96).

During the first years CDAD was acknowledged to exist, the most common cause of CDAD was thought to be previous exposure to clindamycin. A common approach to the affected patients was withdrawal of clindamycin and oral treatment with vancomycin. A majority of the patients had good clinical response, but up to 25% relapsed when ceasing vancomycin (195). Increasingly, broad spectrum cephalosporins and penicillins with beta-lactamase inhibitors were recognized as inducing agents, and lately C-8-methoxy substituted fluoroquinolones have also come into focus (196). Several other patient characteristics like underlying disease, previous hospitalization, age and use of other medication are identified as risk factors for hospital acquired CDAD (197). In addition several institutional characteristics like previous incidence of CDAD and infection control measures should also be accounted for (145, 198). Recent data strongly suggest a weaker association between the consumption of broad spectrum antibiotics and CDAD in connection with a low compared to a high hospital incidence of *Clostridium difficile* infections (196, 198). In addition, several underlying characteristics of the link between consumption of antibiotics and CDAD, including the timeframe for environmental contamination, colonization of patients, subsequent exposure to antibiotics, development of infection, and diagnosis of disease, highlight the need to account for the temporal relationships between several input variables and the emergence of CDAD (145, 198).

There are major concerns about study design in studies assessing consumption of antibacterial agents and hospital acquired CDAD (199). Several examples of methodological flaws due to bias and confounding, choice of inappropriate control groups, misclassification, not accounting for underlying diseases and lack of precision in effect estimates due to insufficient sample size limit the identification and impact of different risk factors for CDAD. Especially, in case-control studies the choice of control group deserves careful attention (200, 201). Cases and controls should come from the same source population, which means that the controls would have been included amongst the cases if they had developed the disease. Restricting the selection of controls to those suspected to have CD invalidates the assumption that the controls are representative for the population from which the cases arose, and enhances the risk that the exposures are similar for all causes of hospital acquired diarrhea or because of misclassification of patients with false negative tests as controls (199). Either case enhances the risk for a biased result towards the null.

Undoubtedly, the association between the consumption of antibacterial agents and hospital acquired CDAC are complex and inputs from different variables may be difficult to interpret. Indeed, the exposure to broad spectrum antibacterial agents is probably of great importance, but the relative contribution from different classes of antibiotics and their temporal effects has yet to be determined.

The epidemiology of CDAD has changed over the last decade. There is evidence suggesting an increasing incidence of hospital related CDAD (202-204), and data from the USA shows an increase in CDAD associated mortality rate from 5,7/million population in 1999 to 23,7/million in 2004. Indeed, there is also evidence that the disease is becoming more refractory to treatment. The change in incidence, the severity of the disease and the refractoriness to treatment are associated to the emergence of a hyper virulent strain (195). Reports on outbreaks caused by this strain have come from a large number of hospitals in Northern America and from hospitals in several countries in Europe. In Norway there has so far only been sporadic isolates of this strain (Gunnar Skov Simonsen, personal communication).

In addition to increasing risk for a prolonged stay at the hospital and a serious outcome of hospitalization, a high incidence of CDAD constitutes a considerable economic burden to the hospital. In Europe, the incremental cost of CDAD is estimated to be in the order of 5 to 15000 euro per case (204). If the hyper virulent strain NAP1/BII/027 becomes endemic, the average cost per case will further increase.

In summary, our study compared data on antibiotic use, infection control facilities and the incidence of CDAD at two tertiary care university hospitals. There are obvious differences between the hospitals considering the patient population, bed occupancy rate, proportion of single rooms, other infection control facilities and choice of antibacterial therapy. Compliance to hand hygienic policies and use of alcohol based hand scrubs were not measured, but a possible effect from alcohol based hand scrubs on the incidence of CDAD is nevertheless uncertain (145). Although we found a lower consumption of broad spectrum antibacterial agents at Aker University hospital, the incidence of CDAD was higher at Aker University Hospital than at the University Hospital of North Norway in Tromsø. This observation highlights the importance of other variables in facilitating the acquisition and spread of CDAD. Another interesting aspect is that our data did not allow accounting for possible temporal relationships between relevant risk factors and the incidence of CDAD. There is a time lag between an increase in the consumption of certain broad spectrum antibacterial agents and an increasing incidence of CDAD, and the incidence of CDAD is also dependent upon the incidence of CDAD the previous months (145, 198).

8.4 Validation of a simplified netilmicin dosage regimens in infants

Streamlining of therapy has received increasing attention in institutional care although this is only a systematic application of professional, persuasive, restrictive and structural interventions. Streamlining may imply use of rapid diagnostic tests, targeting of therapy after identification of the probable causative agent, dose adjustment after therapeutic drug monitoring or to renal function, and dose tapering during treatment.

Aminoglycosides express high efficacy towards a wide range of human bacterial pathogens, and in vitro studies have demonstrated a concentration dependent bactericidal- and post antibiotic effect. Treatment with aminoglycosides implies an increased risk of oto- and renal toxicity to the patient regardless of single or multiple daily dosing regimens, and therapeutic drug monitoring is mandatory. Interestingly, multiple daily dosing of aminoglycosides was universally adopted in both adults and children based on no evidence (205).

A maximum plasma concentration / MIC ratio of 8-10 has been demonstrated to improve therapeutic outcome in life threatening bacterial infections in adults,

minimize bacterial pathogen survival and reduce emergence of resistance. Meta-analyses have documented favorable efficacy, less toxicity, and reduced costs of once-daily dosing regimens versus three times daily regimens in adults (6). Similar conclusions are drawn in two meta-analyses addressing high-dosage extended interval regimens in neonates and children (205, 206), although the incidence of irreversible ototoxicity in children after once-daily dosing is unknown (205). In fact, no adequate long term assessment of the incidence of hearing impairment has yet been reported in studies using extended interval dosing (207).

All aminoglycosides are eliminated renally, and an immature renal function or a renal dysfunction due to tubular damage will decrease renal clearance and increase elimination half-life. The pathogenesis of aminoglycoside nephrotoxicity is directly related to the accumulation of drug within the renal cortex (208), although an affection of the tubular function may occur earlier (209). Nephrotoxicity assessed by elevated levels of creatinin is rare in high dose extended interval regimens, and seldom occurs early in the treatment of neonates (210, 211). Accounting for the limited number of patients (n=11) with plasma creatinin >90 $\mu\text{mol/l}$ in our study, the observation of an association between creatinin levels >90 $\mu\text{mol/l}$ and an increased risk of trough concentration above 2 mg/l should be interpreted with caution. Most of these patients had immature renal functions, and the design of the study did not allow for an assessment of causality between elevated creatinin, netilmicin treatment and other risk factors. A recent study using retinal binding protein and alpha-1-microglobulin as indication of tubular damage and dysfunction, found similar and low rates of nephrotoxicity in once-daily dosing as compared to multiple daily dosing in neonates with a GA below 37 weeks (212).

Bacterial sepsis in preterm neonates is a serious complication commonly treated with a combination of an aminoglycoside and a beta-lactam agent (213). Due to increased extracellular volume and immature renal function in preterm neonates, it is difficult to achieve adequate maximum concentration in combination with a safe trough concentration within a 24 hour dosing interval in this patient group. Some authors have argued that extended intervals may increase the risk of exceeding the duration of the post antibiotic effect and thereby impose a risk for prolonged periods of clinically inadequate drug concentrations, although a clear therapeutic range, and the correlation between serum concentration, efficacy and toxicity is not well established in neonates (213).

Gestational age (GA) and the volume of distribution correlate, but despite keeping the dosage at 6 mg/kg body weight we found no correlation between GA and peak concentration during the first week of life. On the other hand, we found the half-life to be inversely correlated to postnatal age during the first week of life. Assessing pharmacokinetic parameters on the first day of life in preterm neonates, Rengelhausen *et al.* found that systemic clearance and volume of distribution (not normalized to body weight) significantly correlated to birth weight, but not to GA. In a study of amikacin, Allegaert *et al.* found no change in volume of distribution in a cohort of neonates with GA of 24 to 30 weeks on the first day of life. Since both cohorts only included neonates on their first day of life, the authors were precluded to assess postnatal changes in volume of distribution and possible consequences for the elimination half-life. However, clearance approximately doubled from a GA of 24 weeks compared to infants with a GA of 30 weeks (214, 215). On assessing the population parameter variability for clearance with and without covariates, these authors found a lower variability when covariates like body weight and GA were accounted for. Still, approximately 35% of the variability in clearance was unexplained suggesting important impact of other variables (215).

The dosing interval in our study was 24 or 36 hours depending on gestational age, postnatal age, and post menstrual age. In the group with PA 0 to 7 days, and GA <34 weeks, 15/35 patients had a $C_{\min} > 2$ mg/l, strongly suggesting that the 36 hours dosing interval was too short. In a study assessing the elimination of a single dose of 5 mg/kg the first day of life, estimated time to the next dose was 42 hours (213). We found a significant correlation between elimination half-life and GA, but our data also indicate considerable inter-individual variation. This is in accordance with data from other investigators, and probably suggests a limited predictability of aminoglycoside pharmacokinetics in preterm neonates.

In summary, a high-dosage netilmicin dosage regimen with a dosing interval of 48 hours for neonates with gestational age (GA) < 29 week, 36 hours for GA 29 – 36 weeks and 24 hours for full term babies will avoid the majority of trough levels over 2 mg/l, and still provide adequate therapeutic efficacy.

9 Further aspects

As outlined in this thesis, there are shortcomings in existing methods for monitoring and optimizing the use of antibacterial agents. There are also numerous limitations in the understanding of the complex temporal relationship between drug consumption and the emergence of antimicrobial resistance. Below I suggest possible contributions to the identification of causal relations within the field of pharmacoepidemiology of antimicrobials.

Antibacterial agents and interventions

- Standardization of methods.
- Include variables on costs, clinical- and microbial outcomes.
- Assess the sustainability of the interventions.

Antibacterial agents and resistance

- Standardization of methods.
- Further development of methods for investigation of temporal relationships between consumption and resistance. This includes theoretical modeling on the impact of the prevalence of resistant strains, individual versus ecological data, to investigate the significance of applying different adjusting factors in the models.
- Well designed multi-centre studies addressing important clinical question, for example on treatment of community acquired pneumonia.
- Increase focus on clinical and microbial outcomes when implementing interventions.

Antibacterial agents and neonates

- To validate the efficacy of antibacterial dosing regimens for neonates.

Antibacterial agents and *Clostridium difficile* associated diarrhea

- Apply established epidemiological principles when planning future studies. This includes recruiting an adequate sample size, to control for bias and confounding and to select appropriate controls where relevant.

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