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THE ARCTIC
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OF NORWAY

FACULTY OF HEALTH SCIENCES
DEPARTMENT OF PHARMACY

Appropriate antibiotic prescribing in Community-Acquired Pneumonia in a Norwegian hospital setting

June Utnes Høgli

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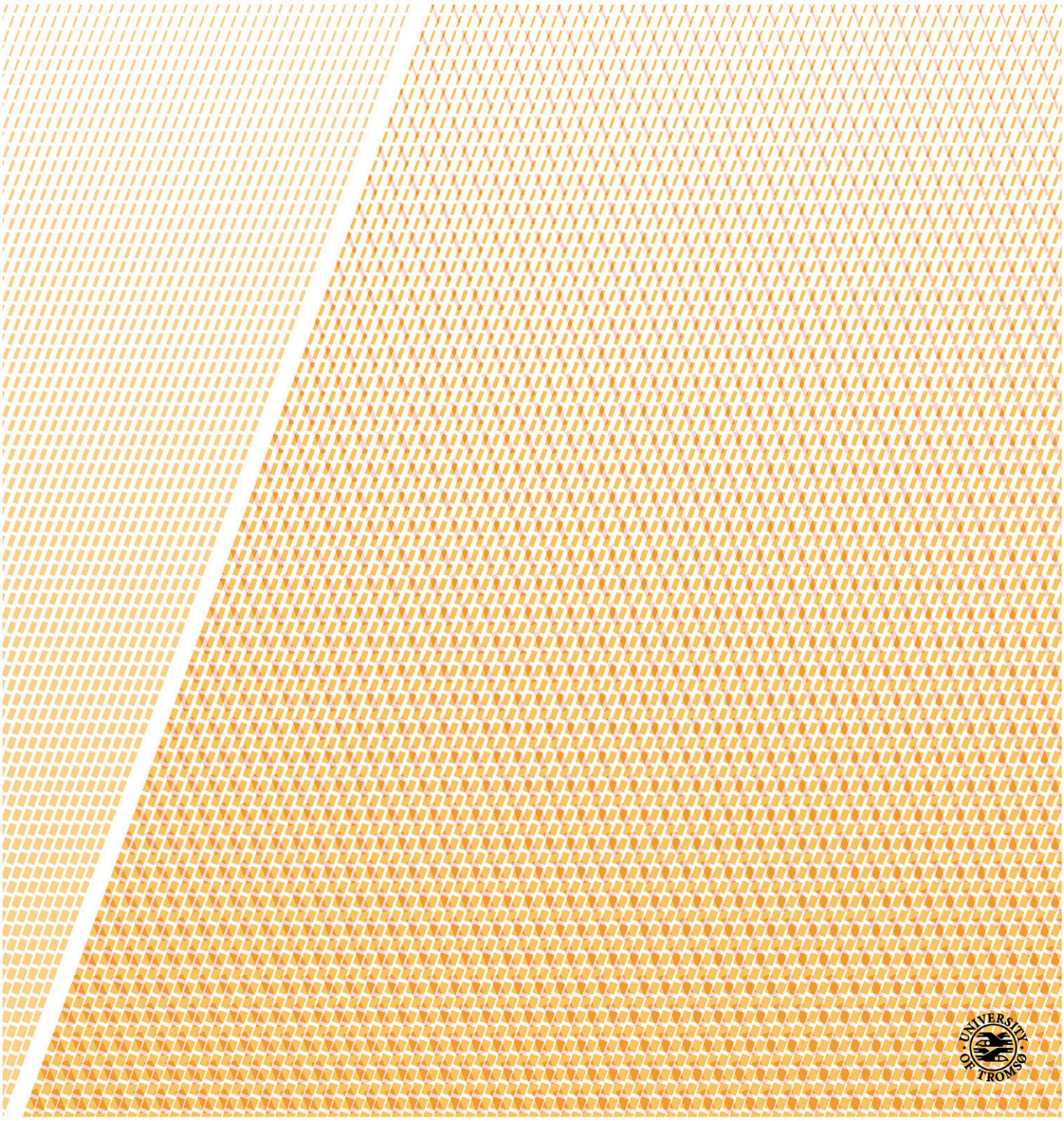

Acknowledgments

Promoting appropriate antibiotic prescribing has really become a matter close to my heart, and I really hope I will get the opportunity to work within this field in the future. I am indebted to all of you that have followed me these years.

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Best regards,

June Utnes Høgli

Tromsø, June 2015

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Scientific environment

June Utnes Høgli and the supervisors were originally members of the research group MMPE (Microbiology, molecular and pharmacoepidemiology) at Department of Pharmacy, University of Tromsø – The Arctic University of Norway. In January 2015, MMPE was divided into two groups: MICRO-POP (Microbial Pharmacology and Population Biology Research Group) and IPSUM (Identify and Prevent Suboptimal Medication Use). June Utnes Høgli and the supervisors are currently members of IPSUM. Initially, Gro Dahlseng Håkonsen and Kaare Magne Nielsen were involved as supervisors for a short period.

Supervisors

Lars Småbrekke, Cand Pharm, MPH and PhD
Associate professor
Department of Pharmacy
UiT – The Arctic University of Norway
9037 Tromsø
Norway

Beate Hennie Garcia, Cand.Pharm and PhD
Associate professor
Department of Pharmacy
UiT – The Arctic University of Norway
9037 Tromsø
Norway

List of papers

PAPER I

Høgli JU, Småbrekke L, Garcia BH. *MAT-CAP: a novel medication assessment tool to explore adherence to clinical practice guidelines in community-acquired pneumonia.* Pharmacoepidemiol Drug Saf 2014;9:933-41.

PAPER II

Høgli JU, Garcia BH, Svendsen K, Skogen V, Småbrekke L. *Adherence to guideline for empirical antibiotics is safe and reduces risk of readmission of hospitalised patients with community-acquired pneumonia in Norway.* [Manuscript, submitted June 2015].

PAPER III

Høgli JU, Garcia BH, Skjold F, Skogen V, Småbrekke L. *An audit and feedback intervention study increased appropriate antibiotic prescribing at a Norwegian hospital*. [Manuscript, submitted June 2015].

Definitions and key concepts

Antimicrobials/antibiotics
A general term for drugs, chemicals or other substances, that either kill or slow the growth of microbes. Among the antimicrobial agents are antibacterial drugs, antiviral agents, antifungal agents, and antiparasitic drugs. This thesis focus on antibacterial drugs, referred to as antibiotics (1).

Antimicrobial resistance/antibiotic resistance (AMR)
Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. AMR comprise resistance to drugs to treat infections caused by bacteria, viruses, parasites and fungi (2).

Antibiotic stewardship program (ASP)
Coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration (3).

Inappropriate prescribing
Prescribing that does not conform to good standards of treatment (not according to Clinical Practice Guideline recommendations) – for example, overprescribing, incorrect prescribing, multiple prescribing, or underprescribing of medications (4).

Audit and Feedback (A&F)
A summary, written or verbal, of clinical performance of health care over a specified period (5).

Clinical Practice Guidelines (CPG) / CPG recommendations
A document that includes a set of statements about appropriate healthcare to support daily practice, based on evidence and critical appraisal, aimed at the explicit statement of good medical practice. A systematically developed statement to assist the practitioner in decision making about appropriate healthcare for specific clinical circumstances (6).

Community-Acquired Pneumonia (CAP)
Pneumonia that is acquired outside hospital. Pneumonia acquired in nursing home residents is included in this definition in this thesis.

Defined daily dose (DDD)
The assumed average maintenance dose per day for a drug used for its main indication in adults (7).

Length of stay in hospital (LOS)
The period of time a patient remains in hospital, counted from day of admission to day of discharge (i.e. based on the number of nights spent in hospital) (8).

Medication Assessment Tool (MAT)
A MAT is a set of evidence-based review criteria to be used for assessing the level of adherence between CPG recommendations and clinical performance in a particular therapeutic field (9). *Original MAT-CAP* is addressed as the tool developed in Paper I, while *simplified* MAT-CAP is addressed as the tool applied in Paper II.

Quality Indicator (QI)
A measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality, of care provided (10).

Review criteria/ MAT criteria
Systematically developed statement relating to a single act of medical care that is so clearly defined it is possible to say whether the element of care occurred or not retrospectively in order to assess the appropriateness of specific healthcare decisions, services, and outcomes (10).

Total duration of antibiotic treatment
In-hospital treatment plus estimated length of treatment based on prescription of antibiotics at time of discharge. In this thesis, treatment started pre hospitalization is not included in the calculation of total duration.

30-day mortality
Mortality ≤30 days, counted from date of admission. In this thesis we measure all-cause mortality.

30-day readmission
Readmission ≤30 days, counted from date of discharge. In this thesis we measure unplanned readmission of any cause.

Abbreviations

AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
A&F	Audit and Feedback
AMR	Anti-Microbial Resistance
ASP	Antibiotic Stewardship Program
CAP	Community-Acquired Pneumonia
CBA	Controlled Before-After study
CCT	Controlled Clinical Trial
CPG	Clinical Practice Guideline
CRB-65	Confusion, Respiration, Blood pressure and age 65 or more
CURB-65	Confusion, blood Urea nitrogen, Respiration, Blood pressure and age 65 or more
DAG	Directed Acyclic Graph
DCF	Data Collection Form
DDD	Defined Daily Dose
DID	DDD per 1000 inhabitants per day
ECAC-net	European Surveillance of Antimicrobial Consumption Network
ED	Emergency Department
GFR	Glomular Filtration Rate
haDDD	hospital-adjusted DDD
ICD-10	The International Classification of Diseases (version 10)
IDq	Insufficient Data to decide if the qualifying statement is applicable
IDs	Insufficient Data to decide upon the response of the standard
ITS	Interrupted Time Series design
LOS	Length Of hospital Stay
MAT	Medication Assessment Tool
MAT-CAP	Medication Assessment Tool for Community-Acquired Pneumonia
MIC	Minimum Inhibitory Concentration
NA	Not Applicable
NORM	Norwegian Surveillance Programme for Antimicrobial Resistance in human pathogens
PPS	Point-Prevalence Study
PSI	Pneumonia Severity Index
QI	Quality Indicator
RCT	Randomized Controlled Trial
SIRS	Systemic Inflammatory Response Syndrome
UiT	University of Tromsø - The arctic university of Norway
UNN	University Hospital of North Norway
WHO	World Health Organization

English summary

Appropriate antibiotic prescribing is associated with favourable levels of antimicrobial resistance and clinical outcomes. Literature has indicated that antibiotic treatment of hospitalised patients with community-acquired pneumonia (CAP), the leading cause of death due to infection in adults worldwide, have potential for improvement. Interventions for increasing appropriate antibiotic treatment in the Norwegian hospital setting are requested.

The overall aim of this PhD-work has been to promote appropriate antibiotic prescribing in hospitalised patients with CAP. The thesis addresses this in three different papers. First, the thesis presents design and validation of a Medication Assessment Tool for CAP (MAT-CAP) for retrospective audit of antibiotic prescribing at the University Hospital North Norway (UNN). Consequently, areas with low and high quality of prescribing can be identified. Especially areas with low quality of prescribing can tailor future interventions. Second, the thesis describes the association between adherence to Norwegian guideline recommendations and mortality, risk of readmission and prolonged length of stay for inpatients with CAP. Third, this thesis presents an intervention study performed at a respiratory medicine department where we tailored improvement of empirical antibiotic prescribing, reduction in use of high-dose benzylpenicillin and reduction in total treatment duration.

MAT-CAP was developed and content validity, reliability and feasibility was demonstrated. We identified that adherence to guideline on empirical antibiotic was high, safe and associated with reduced risk of readmission to hospital within 30-days in a selective group of CAP-patients admitted to UNN. Our findings support the Norwegian guideline recommendations, and demonstrate the importance of having guidelines adapted to local and national levels of antimicrobial resistance. Further, we identified a prolonged duration of intravenous administration and total treatment duration with potentials for reduction. In an audit and feedback intervention study combined with distribution of a pocket version of the national antibiotic guideline, prescribing of appropriate empirical antibiotics substantially increased as a consequence of the intervention, and the effect sustained six months post intervention. However, for reducing total treatment duration and achieving dosage optimization of benzylpenicillin additional prospective interventions are warranted.

1. Introduction

1.1 Appropriate and inappropriate antibiotic prescribing

Antibiotics have significantly reduced morbidity, mortality, as well as costs related to infectious diseases, and have allowed advances in modern medicine in relation to surgery and cancer treatment (11, 12). However, increasingly accelerating levels of antimicrobial resistance (AMR) threatens the value of antibiotics. Although AMR is a natural phenomenon, there is solid evidence that antibiotic use is the major impetus for development of AMR (13, 14). Poor infection control, inadequate hygienic standards and inappropriate food handling accelerates spread of AMR (2). Furthermore, inappropriate antibiotic prescribing (and use) is linked to unfavourable health care costs and clinical outcomes such as adverse events, length of hospital stay (LOS), readmission, morbidity and mortality (15, 16).

Clinical practice guidelines (CPGs) are developed and implemented in order to improve the quality of care, to support health care decisions and to diminish unwanted diversity of practice (17). Appropriate antibiotic treatment is reflected by recommendations in CPGs, and involves choice of therapy, dose, and duration of treatment. Promoting appropriate prescribing of antibiotics is essential for reducing emergence of AMR, reducing health care costs and patient safety (18).

1.1.1 Potential causes of inappropriate antibiotic prescribing and use

Potential causes for patient-, prescriber-, culture- and health care related factors contributing to inappropriate prescribing and use of antibiotics are listed in Table 1. Interventions for promoting appropriate antibiotic prescribing must target potential causes, and be directed towards correct group and setting (19).

Table 1: Potential causes of inappropriate prescribing and use associated with patient-, prescriber-, culture- and health care related factors (19-24).

Patient-related factors	Prescriber-related factors	Culture-related factors	Health care related (structural) factors
Lack of public knowledge about antibiotics and infections; i.e. difference between viral and bacterial infection and consequences of antibiotic use	Prescribing of antibiotics for self-limiting infections	Social norm and culture for prescribing and receiving antibiotics	Lack of rapid point-of-care diagnostic test
Expectations on receiving antibiotics	Perceived expectations from patients	Behaviour and attitude	Marketing and advertisement towards prescribers and public
Poor compliance	Lack of knowledge or training in prescribing antibiotics	Hierarchical societies tend to have higher use of medicines compared to egalitarian society	Possible to buy antibiotics "over-counter" and internet. Counterfeit antibiotics
Use of leftovers and sharing antibiotics	Not up-to date on recent clinical practice guideline recommendations		Lack of surveillance, strategies and interventions. Suboptimal coordination and cooperation Financial; Incentives from the medical industry. Health care funding of certain antibiotics Abridged availability of vaccines; increased use of antibiotics Number of antibiotics registered

1.1.2 Surveillance and audit of antibiotic prescribing

Detailed information on antibiotic consumption is important for optimizing treatment strategies (25). Different methods applied in order to assess quality of antibiotic prescribing, with focus on hospital setting, are described below.

Aggregated data

Pharmacy sales data or wholesale data are the main sources of aggregated data, and is an important supplement to prescription data (25). Data is readily available and can provide awareness of quality of prescribing, trends can be assessed and countries and settings can be compared. A major drawback is that consumption data is only a rough estimate of consumption not providing exact use, and appropriateness of prescribing, measured with other

methods, provides a stronger link between process and outcome compared to consumption data (7, 26).

Although hospital treatment only contributes with 10-20% of total human antibiotic consumption, hospitals are main reservoirs for emergence and spread of AMR (27). Hospital treatment often includes broad-spectrum antibiotics such as third generation cephalosporines, carbapenems and quinolones. From the outpatient setting, it is established that countries with high antibiotic consumption tend to have high level of AMR (28).

In hospital, antibiotic consumption is often reported as number defined daily doses (DDD)/100 bed days, or DDD/100 admissions or discharges to adjust for clinical activity (29, 30). While DDD/ 100 bed days are sensitive for variations in LOS, DDD/100 admission or discharge is sensitive for change in number of admissions/discharges. Consequently, both should be reported concurrently. In Europe, surveillance of antibiotic consumption in hospital has not been fully established. The European Society of Antibiotic consumption network (ESAC-net) still provides consumption data for hospitals in form of doses per 1000 inhabitants per day (DID) (31). DID is not an optimal measure in the hospital setting due to difficulties in defining "inhabitants" (i.e. the hospital population) (32). In addition, discrepancies between doses recommended for hospital setting and outpatient setting are common. ESAC-net has settled a working group on developing and implementing unique hospital protocols for collecting and reporting antibiotic consumption (31). Recently, Haug *et.al* suggested hospital-adjusted defined daily doses (haDDDs), where DDD are adjusted to doses recommended for inpatients (29). By applying haDDDs, the authors found that for penicillins the classic DDD-calculation produced skewed findings of antibiotic consumption, and suggested haDDD as supplement to DDD in future.

In Europe in 2013, the antibiotic consumption in hospital ranged from 1.1 DID in the Netherlands to 2.46 DID in Italy (Finland had DID of 2.79, but data comprised nursing home and health care centres). Consumption according to antibiotic classes also varies among countries; the proportion of fluoroquinolone ranged from 6% in Norway to 19% in Italy (33). In Norway, antibiotic consumption data are published annually through the Norwegian Surveillance Programme for Antimicrobial Resistance in Human Pathogens (NORM)-report (outpatient and hospital consumption). In 2013, overall sales of antibiotics to Norwegian hospitals were 1.4 DID and penicillins accounted for 46% (J01C) (34).

A study including eight hospitals in east of Norway, revealed a total antibiotic increase from 1.02 DID to 1.30 DID and from 61.7 to 72.4 DDDs/100 bed days in the period 2002-2007 (35). The same study described a total increase of broad-spectrum antibiotics of 47.9% when measured as DDDs/100 bed days. The authors raised concern about increasing broad-spectrum antibiotic use (i.e. unjustified use) considering the low prevalence of AMR in Norway (35). In data from 2006-2011, total antibiotic use in Norwegian hospitals was 67.1 DDD/100 bed-days and 49.3 haDDD/100 bed days (29). During 2006-2012, the consumption of cephalosporines and carbapenems increased in three out of four health regions in Norway (36). In a Danish study the authors share the same concerns on the increased use of broad-spectrum treatment (37).

Point prevalence studies

Point prevalence studies (PPS) relate antibiotic treatment to the individual patient at a chosen time. PPS allows collection of infection-related information as indication and doses. PPSs are easy to perform according to standardized protocols, and require limited resources. One to two PPS per year is reported as sufficient to provide monitoring of antibiotic use. Repeated PPS (over years) can identify trends and can provide feedback to clinicians, guide and assess effects of interventions. PPS can also be used in benchmarking, i.e. comparing hospitals nationally and internationally. The limitation of PPS is reduced ability to take longitudinal incidence data into account, as well as reduced ability to link findings provided by PPS to outcome measures (38-40). Performance is often reported in form of proportions.

In a survey by ESAC-net member countries in 2009, adherence to guideline was 62.0 % – which ESAC-net finds low (41). During 2011-2012 ESAC-net performed an EU-wide PPS among 1149 acute care hospitals in all member states. The overall prevalence of antibiotic use was 32.7% (95% CI; 29.4-36.2%). Some key findings; 70.9% of patients received one antibiotic agent, 70.6% of the antibiotics were administrated intravenously, indication was noted in 79.4% of the patients medication charts, and community-acquired infections was the most frequent indication (pneumonia accounted for 23.8%). Amoxicillin with enzyme inhibitor was the most frequently prescribed antibiotic accounting for 11.8%, followed by ciprofloxacin and ceftriaxone. Benzylpenicillin, which is widely used in Norway, was the third lowest prescribed antibiotic. ESAC-net identified several areas with potential for improvement; e.g. reduce use of broad-spectrum antibiotics, use of single dose for surgical prophylaxis and reduce duration on intravenous treatment (42). The Norwegian participation

in the 2011-2012 survey was low; only 7 of 60 acute care hospitals participated (12%). However, some PPS have been performed in specific Norwegian hospitals (43, 44), including measuring effect of interventions (45, 46).

Incidence studies

In incidence studies patients are followed over time and data allows assessment of association between performance and outcome. As the method is time consuming and resource demanding, most incidence studies are performed as time-limited audits. In future, more adequate IT-systems can be a solution on this concern (i.e. electronic medication charts where data can be extracted automatically from patient records). In incidence studies, performance is often reported in form of proportion such as percent adherence to CPG.

1.1.3 Measuring appropriateness of prescribing with different incidence methods

Quality registers

”Quality registries contains individualized data concerning patient problems, medical interventions, and outcomes after treatment; within all healthcare production” (47). The aim is to cover all patients with a certain condition or who are subject to a specific treatment or belong to a certain risk group. In Sweden, seven national quality registers have been established within infectious diseases and antibiotic treatment. To illustrate the value of quality registers, data from the Swedish CAP-register was recently applied to demonstrate reduced mortality among non-severe patients prescribed benzylpenicillin in monotherapy compared to other (inappropriate) antibiotics (48).

Quality indicators

Recommendations in CPGs can be transformed to quality indicators (QIs). QIs can identify high, intermediate and low quality of prescribing. Especially low quality of prescribing, can tailor need for intervention. QIs can also be applied to measure effect of interventions, in surveillance and for benchmarking. Moreover, with QIs appropriateness of treatment (i.e. adherence to guideline) can be explored and association between adherence to CPG recommendations and clinical outcome can be tested. Majority of QIs developed for the hospital setting are infection specific, such as QIs for urinary tract infections, sepsis and community-acquired pneumonia (CAP) (49-52). To illustrate utilization of QIs, in the Netherlands Spoorenberg *et al*. demonstrated that adherence to CPG recommendations on

empirical selection in hospitalised patients with urinary tract infection was low (46.3 % adherence to local CPGs and 65.6 % to national CPG). At the same time they also demonstrated that adhering to CPG was associated with reduced LOS (53).

Recently, van den Bosch and colleagues suggested eleven generic QIs to measure appropriate antibiotic use in the hospital setting, see Table 2 (54). The 11 QIs cover various steps along the antibiotic pathway. The aim of developing and applying generic QIs is that hospitals can perform continuously self-monitoring and improvement of antibiotic use (54), and measuring effect of antibiotic stewardship programs (ASP, described in detail in section 1.2.2). Also in Germany it has recently been developed QIs for evaluating implementation of ASP (55). These generic QIs are currently being tested in clinical practice (56).

Table 2: Generic quality indicators, developed by van den Bosch *et al*, to measure appropriate antibiotic use in hospitals (54).

No.	Quality indicator
1	Empirical systemic antibiotics should be described according to (local) guideline.
2	Before starting systemic antibiotic therapy at least 2 sets of blood cultures should be taken.
3	When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started.
4	Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available.
5	Dose and dosing interval of systemic antibiotics should be adapted to renal function.
6	Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate.
7	An antibiotic plan should be documented in the case notes at start of systemic antibiotic treatment (Antibiotic plan is indication, name, doses, route, and interval of administration.)
8	Therapeutic drug monitoring should be performed when the treatment duration is >3 d for aminoglycosides and >5 d for vancomycin.
9	Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be 7 d.
10	A current local antibiotic guideline should be present in the hospital and an evaluation whether an update should be considered should be done every 3 y.
11	Local antibiotic guidelines should correspond to the national antibiotic guidelines, but should deviate based on local resistance patterns.

Medication Assessment Tool (MAT)

MAT is a tool applied for assessing appropriateness of drug use in relation to CPGs. It is designed to be explicit, meaning that quality of prescribing is assessed with limited possibilities for subjective clinical judgments. The intention of a MAT is to be applied routinely in a clinical setting as a checklist for clinicians or to measure CPG adherence and to identify changes in adherence over time. Currently it exist MATs for assessing drug treatment

of cardiovascular diseases, cancer pain management, asthma and rheumatoid arthritis (57-62). The various MATs share the same overall structure, and are operationalized with support of an application guide listing justified reasons for not prescribing in adherence with CPG. In MAT methodology, we transform QIs into review criteria (also called MAT criteria) that can be answered 'yes' or 'no', reflecting adherence or non-adherence with CPG recommendations. For details, see Box1. In most of the MATs, it is operated with > 75%, 50-75% and < 50% as high, intermediate and low adherence, respectively (63, 64).

Box 1: Medication Assessment Tool criteria and adherence calculation (57, 59, 60).

A MAT criterion consists of a combination of two statements: a 'qualifying statement' (q) followed by a 'standard' (s). The *qualifying statement* determines whether the criterion is applicable in the specific patient. If the qualifying statement is not applicable, the response alternative is 'NA' (not applicable). In cases with insufficient data to decide whether the criterion is applicable, we choose the response alternative IDq (insufficient data to answer the qualifying statement). The *standard* can be tested if the criterion is applicable. If clinical practice is in accordance with guideline, the answer to the standard is YES and adherence is identified. If it is not, the answer is NO, and non-adherence is identified. In some patients, there may be a justified reason for non-adherence, which is accounted for in MAT methodology by the response alternative Nj (justified reason for non-adherence). In cases with insufficient data to answer the standard, we choose the response alternative IDs (insufficient data to answer the standard). In other words, IDq and IDs document extent of insufficient data in patient records. Adherence to guideline is calculated by summing YES responses and expressing them as percentage of applicable cases (YES + NO + Nj + IDs). Adherence can be expressed for single criteria and on an overall basis.

Table: Examples of criteria in a Medication Assessment Tool

Tool	Qualifying statement	Standard
Garcia *et al.*	Patient with established CHD	*Is prescribed aspirin*
Liu *et al*.	Patient with exercised-induced asthma	*Is prescribed LRA, LABA, chromones, or theophyllines*

CHD; Coronary heart disease, LRA; leukotriene receptor antagonist, LABA; inhaled long-acting β2-agnist

1.2 Interventions promoting appropriate prescribing in hospitals

A diverse range of campaigns and strategies has been developed the recent years. To exemplify, the ESAC-net has developed public health initiatives as the European Antibiotic Awareness Day, an annual event taking place on November 18th to raise focus on appropriate antibiotic treatment and AMR. Both prescribers and the public have been targeted. In US and UK, they have implemented the "Get Smart for Healthcare"- and "Start Smart-Then Focus"-program, respectively (65, 66). In Norway in 2011, the National Centre for Antibiotic Use in Hospital was established as a part of the Norwegian strategy to promote appropriate antibiotic prescribing in Norwegian hospitals (67). In 2013, a national CPG for antibiotic prescribing in hospital was published online, followed by a pocket version which was published and distributed 2014 (68).

1.2.1 Types of interventions, effect and outcome

Interventions to improve antibiotic prescribing are mainly divided into persuasive, restrictive and structural (69). Persuasive interventions is about advising other physicians in form of distributing materials, arranging meetings, outreach visits, audit and feedback (A&F), and reminders. Restrictive interventions involve restricting prescribers' freedom to prescribe specific antibiotics. Structural interventions involve regulatory measures, new routines and technology (69).

A recent Cochrane review explored the effect of interventions to improve antibiotic prescribing in hospital settings (69). The review comprised randomized control trials (RCTs), controlled clinical trials (CCTs), controlled before-after studies (CBA) and interrupted time series studies (ITS). Eighty-nine studies were included, where 56 studies were ITS, 25 RCT, 5 CBA and 3 CCT. Eighty-four of the studies targeted choice of antibiotic, timing of first dose or route of administration. The remaining targeted decision to treat or duration of treatment. For ITS, median change in prescribing was 42.3% and 34.7% for persuasive and restrictive interventions, respectively. In general, median effect was higher measured by ITS compared to RCTs, CCTs and CBA. Restrictive interventions are found to have greater impact on prescribing than persuasive interventions at one month after implementation, but at six months and beyond they are equally effective (69). Interventions comprising decision to treat and duration of treatment were linked to reduction in microbiological outcomes. For mortality, the Cochrane review revealed that interventions in hospital either had no impact on

mortality or gave a significant reduction in mortality. Only one Norwegian study was included in the Cochrane review (45). Intervention studies originating from the Norwegian hospital setting are requested (70).

1.2.2 Antibiotic stewardship programs

ASP is the set of activities and polices implemented to promote and improve appropriate use of antibiotics, and they are often employed simultaneously (71). The aim of ASP is to improve patient care and outcome, lowering unintended adverse effects, promoting cost-effectiveness, and reducing or stabilizing level of AMR (72). See Table 3 for an overview of activities and policies that can be included in an ASP.

ASP depends on a multidisciplinary approach, and core members often include an infection disease physician, a clinical microbiologist and a clinical pharmacist, with close cooperation with infection control professionals, hospital epidemiologists and information system specialists. In order to have resources and authority, ASP must be supported by the hospital administration.

It is clear evidence that ASP, in combination with infection prevention and control methods, have positive effective both on appropriateness of prescribing, costs, adverse effects and AMR (26, 73-77). However, developing and implementing ASP in specific hospitals depends on local demands. Factors as available resources, pattern of antibiotic use, patient characteristics, potential outbreaks or current problematic areas will guide the content of the local ASP. Both persuasive and restrictive interventions have advantages and limitations. For many hospitals persuasive interventions are preferred, but restriction have proven to be effective for instance during outbreaks due to a higher immediate effect compared to persuasive interventions (69).

Table 3: Description of activities and polices included in antibiotic stewardship programs (72, 78-80).

Activity	Example	Type of intervention	Advantages and disadvantages - Comments	**Example studies**
Clinical practice guidelines	Development, implementation and enforcement. Local and national guidelines based on microbiology and resistance pattern, in addition to be evidence based	Persuasive	May improve the quality of care, support health decisions and diminish unwanted diversity. Implementation is facilitated through education and feedback on antibiotic use and outcome.	(46, 81-83)
Education	Education of physicians in group or individually Presentations, student and staff teaching sessions, provision of written guidelines or e-mail alerts	Persuasive	Influences behaviour positively, but not effective alone. Marginal and low sustainable effect on antibiotic prescribing. Should be incorporated into other activities.	(84, 85)
Audit and feedback (A&F)	Prospective: Daily review of targeted antibiotic therapy (i.e. switch, streamlining/de-escalation, dose optimization, monitoring) Direct contact with prescribers for discussion and recommendations Retrospective: audit of adherence	Persuasive	May influence both process measures and clinical outcome measures – but effect often rely on level of quality at start of the intervention. Has educational effect and allows prescribers to maintain autonomy. Effect relies on good communication with prescribers. Necessary to identify the patients with inappropriate treatment.	(86-88)
Restriction	Restriction of targeted antibiotics Requiring approval pre-prescribing (applying order forms)	Restrictive	Effective in controlling outbreaks, reducing total consumption and cost. Challenges with staff requirements, risk of delayed start of treatment, resistance for alternative antibiotics can increase, prescriber loses autonomy	(89, 90)
Computer assistance	Clinical decision support Electronic medication chart New routines for laboratory testing	Structural	Point of care; provides patient-specific data important for prescribing. Time and resource demanding implementation of the system.	(91, 92)
Antimicrobial cycling	Rotation of antibiotics used in hospital or on the department/ward	Structural	Potential reduction of resistance by changing elective pressure, but reintroduction is likely to increase resistance again. Risk of increasing costs. Relaying on prescriber being up-to-date on current list/scheduled antibiotic. Many patients excluded do to justified reasons as allergy and toxicity. Insufficient evidence on benefit.	(93, 94)

1.3 Community-acquired pneumonia

CAP is associated with high incidence, morbidity, mortality and health care costs (95-97). The infection mainly affects the elderly, which implies increasing incidence the next decade due to an ageing population.

Streptococcus pneumoniae is the most frequently isolated pathogen, followed by *Haemophilus influenzae, Mycoplasma pneumoniae, Legionella spp* and viruses (96, 98, 99). However, in up to 50% of patients no pathogen is identified. Resistance to *S.pneumoniae* threatens the effect of antibiotic treatment of CAP in many countries. In Europe, for *S.pneumoniae* resistance to penicillin varies between 1.1% in the Netherlands to 40% in Cyprus. For macrolides, it range between 1.5% in Latvia to 38.1% in Romania (100). In US in 2001-2005, the prevalence of multidrug-resistant *S.pneumoniae* was 25% (101). In the recent Centres of Disease Control and Prevention report (from US), it was estimated that in 30% of severe cases, *S.pneumoniae* is resistant to ≥ 1 antibiotics (1). Dual beta-lactam/macrolide resistance is recognized as an increasing problem (1, 18, 100).

The first CPG for CAP was published in Canada in 1993. The following years organizations as the American Thoracic Society/Infectious Diseases Society of American, European Society of Clinical Microbiology and Infectious Diseases, British Thoracic Society and Swedish Society of Infectious Diseases Society, among others, have developed CPGs for CAP (102-105). Level of AMR among common pathogens and treatment traditions are reflected in CPG recommendations, and one international CPG will not fit all countries. To illustrate, in US combination of a beta-lactam and a macrolide, or a fluoroquinolone in monotherapy, is recommended as first-line empirical treatment (102). In Scandinavian countries, US regimes would be considered as overuse.

Disease severity tools are applied to predict mortality and consequently guide both level of care and antibiotic treatment. In US, the Pneumonia Severity Index (PSI) is used for assessing disease severity, while most European countries applies algorithms based on Confusion, Urea, Blood Pressure and Age ≥ 65y (CURB-65), or CRB-65 which is a simplified version of the CURB-65 not requiring laboratory tests (i.e. urea). To illustrate the utilization of severity tools; patients with low risk of mortality (CRB-65 0-1) may be treated in outpatient setting, but if admitted to hospital the Norwegian CPG recommends benzylpenicillin in monotherapy

(68). Patients with high risk of mortality (CRB-65 3-4) may be potential candidates for admission to intensive care units, and in the Norwegian CPG patients with CRB-65 score 3-4 are recommended benzylpenicillin in combination with gentamicin, or as second choice cefotaxime. Macrolide is added if atypical pathogens such as *M.pneumoniae* are suspected (68).

Inappropriate antibiotic prescribing in CAP patients has been related to all aspects of antibiotic treatment (84, 106-108). Numerous studies have showed a positive association between adherence to CPGs and clinical outcomes as mortality, readmission and LOS. However, most of these studies are from countries with high level of AMR (15, 16). To our knowledge, for Norwegian inpatients with CAP association between adherence to CPG and clinical outcomes has not been tested.

2. Aim and objectives of the thesis

The overall aim of this thesis was to promote appropriate antibiotic prescribing in hospitalised patients with CAP.

Paper I

To establish a valid and reliable tool for audit of antibiotic prescribing in hospitalised patients with CAP.

Paper II

To explore the association between adherence to CPG recommendations and mortality, risk of readmission and LOS for inpatients with CAP.

Paper III

To promote appropriate antibiotic prescribing in patients with CAP or acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

3. Materials and methods

3.1 Overview

The thesis is based on three papers;

I. MAT-CAP: a novel medication assessment tool to explore adherence to clinical practice guidelines in CAP
II. Adherence to guideline for empirical antibiotics is safe and reduces risk of readmission of hospitalised patients with community-acquired pneumonia in Norway.
III. An A&F intervention study increased appropriate antibiotic prescribing at a Norwegian hospital.

The studies are conducted at the University Hospital North Norway (UNN), which comprises three hospitals located in three different towns (UNN Harstad, UNN Narvik and UNN Tromsø). UNN in total has about 500 somatic beds, is the leading health care provider in the North Norwegian health region, and serves about 190 000 inhabitants.

An overview of design, setting and study participants is given in Table 4.

Table 4: Design, setting and study participants

Paper	Design	Setting	Population/participants
I	Design and validation; content validity (Delphi study), reliability and feasibility	Internal medicine departments, UNN Harstad, Narvik and Tromsø	Delphi; 6 physicians Reliability: Two pharmacists
II	Retrospective patient-record study	Internal medicine departments, UNN Harstad, Narvik and Tromsø	651 patients included
III	Audit and Feedback intervention study; interrupted time series design	Department of Respiratory Medicine, UNN Tromsø	Department physicians, 253 and 155 patients included pre-and post-intervention, respectively

UNN; University Hospital North Norway

3.2 Paper I

We developed QIs from the local CPG for UNN (109), with support from international CAP-specific CPGs (102, 105, 110). By e-mail we invited 25 physicians, comprising junior registrars and senior consultants with experience within infection, microbiological or internal medicine, from UNN Tromsø, Harstad and Narvik to participate in a two-round modified Delphi study. We asked the physicians to rate each QI on a five-point Likert scale where one was 'not agree' and five was 'strongly agree'. In addition, they were encouraged to comment on the QIs, propose modifications or suggest new QIs. If a QI was rated as four (i.e. agree) or higher by $\geq 75\%$ of the physicians, content validity was demonstrated. QIs not achieving content validity in round one, were subjected for Delphi round two. In round two, we requested them to re-rate the QIs on the basis of information as mean score, range, their own score and comments provided from Delphi round one. QIs with demonstrated content validity were reformulated into review criteria to comply with MAT methodology. An application guide for the novel tool Medication Assessment Tool for Community-Acquired Pneumonia (MAT-CAP) was developed to facilitate application. In order to test feasibility and applicability of MAT-CAP, we performed test on clinical data from a limited number of patient records. Table 5 shows inclusion and exclusion criteria for the study population. Relevant data was extracted from patient records to individual data collection forms (DCF). MAT-CAP was applied on data in the DCF. For MAT-CAP, we explored applicability both on criterion level and overall. In addition, we measured time usage for extraction of data from patient record to DCF and for application of MAT-CAP on data in DCF. In order to demonstrate reliability of MAT-CAP, we performed inter- and intra-rater tests; inter-rater reliability was assessed by two different pharmacists applying MAT-CAP on the same study population, while intra-rater reliability was assessed by one pharmacist applying the MAT-CAP twice with 9 weeks in-between. In the test on clinical data we also calculated adherence on criterion level and overall. Student's *t*-test was used to explore differences in application time between the observers. A p-value <0.05 was considered significant. Reliability was calculated by Cohen's kappa, κ, considering κ scores of ≥ 0.75 as excellent agreement (111). Adherence was reported in percentage with 95% confidence interval. Appendix A gives an overview of specific MAT-related calculations and interpretation.

Table 5: Patient flow; inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• ICD-10 codes J13-J16+J18 • ≥ 18 years of age	• Non-confirmed chest x-ray • Aspiration or nosocomial infection • Immunosuppression/ malignity (i.e. transplanted, cancer, receiving cytostatic medications, human immunodeficiency virus and immunodeficiency with antibody defects • Suspected or confirmed co-infection • Discharged from surgical departments • Consecutive admissions current year • Missing symptoms of infection*

* An exclusion criteria which was applied in Paper I, but not in Paper II
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Pneumonia due to J13; *Streptococcus pneumoniae*, J14; *Hemophilus influenzae*, J15.0-J15.6; *Klebsiella pneumoniae, Pseudomonas, ,staphylococcus, other stretpococci, Escherchia coli* or other Gram-negative bacteria, J15.7; *Mycoplasma pneumoniae*, J15.8; Other specified bacteria, J15.9; Unspecified bacterial pneumonia, J16; Chlamydia pneumoniae and other specified organism, J18: Bronchopneumonia, unspecified organism

3.3 Paper II

Patients discharged from UNN Harstad, Narvik or Tromsø during 2010 and 2012 with ICD-10 codes for pneumonia were eligible for the study. Inclusion and exclusion criteria are given in Table 5. For each included patient, we retrospectively extracted the following predefined patient information from electronic admission and discharge records, medication charts and laboratory data: age, gender, antibiotic use pre-hospitalization, nursing home residency status, time of admission, penicillin allergy status, smoking status, comorbidities, complete antibiotic medication list, infection-relevant laboratory and clinical data, microbiological tests ordered and pathogens identified. Based on data on admission, we calculated severity according to CRB-65 (112, 113) and SIRS (systemic inflammatory response syndrome) (114). Data was denoted into standardized patient specific DCFs. Clinical outcome measures included LOS, 30-day mortality and 30-day readmission.

The original 15-item MAT-CAP was adapted to fit the aim and objectives of Paper II. Consequently, seven criteria (C1-C7) was included in Paper II, allowing us to test the following: timing of first dose, empirical treatment, documentation in patient records if empirical treatment is amended during first 3 days after initiated treatment, microbiological diagnostics, pathogen directed treatment, timing of switch from intravenous to oral antibiotic and total duration of treatment. The simplified MAT-CAP was applied on data in DCF, and applicability, extent of missing information in patient records and adherence to CPG were

reported. See Appendix B-D for DCF, simplified MAT-CAP (i.e. how the criteria relate to the original MAT-CAP published in Paper I) and application guide for the criteria in the simplified MAT-CAP, respectively.

Adherence was reported as percentage with 95% CI. High adherence was defined as >75%, intermediate as 50-75% and low adherence as < 50%. Directed Acyclic Graphs (DAG) methodology was applied to identify covariates to include in the statistical model choosing the minimal adjustment set, see Appendix E and F. Linear and logistic regression analyses were applied to test the association between adherence to CPG and LOS and 30-day readmission, respectively. Findings were reported with 95% CI.

3.4 Paper III

We conducted a three-phase A&F intervention study at an 18-bed respiratory medicine department at UNN Tromsø. All patients discharged with CAP or AECOPD and treated with antibiotics were eligible for the study. Patients with co-infections, nosocomial infection or infection due to aspiration were excluded.

For each included patient we retrospective evaluated if antibiotic treatment was in accordance with national CPG recommendations (68), see Table 6 for an overview of key recommendations. We focused on empiric antibiotic choice, dose and treatment duration. Specifically, we targeted use of empirical antibiotics, categorizing the prescribing as either appropriate (i.e. benzylpenicillin in monotherapy, in combination with gentamicin, or amoxicillin/ampicillin in monotherapy) or inappropriate (i.e. all other antibiotics). Change in prescribing from appropriate to inappropriate antibiotic during first 3 days and during the entire hospital stay was measured, but not targeted for intervention. We targeted dose of benzylpenicillin (i.e. high-dose 3.0 gram x 4 to low-dose 1.2 gram x 4), and treatment duration was calculated as inpatient treatment plus length of prescription at discharge.

Table 6: An abbreviated overview of the Norwegian clinical practice-guideline recommendations for hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and community-acquired pneumonia (CAP)

Infection	Drug	Dose	Duration
AECOPD	Benzylpenicillin (intravenous) Ampicillin (intravenous) Amoxicillin (oral)	1.2 gram x 4 1.0 gram x 4 500 milligram x 3	5 days
CAP Non-severe pneumonia	Benzylpenicillin (intravenous)	1.2 gram x 4	5-7 days
CAP Severe pneumonia CRB-65 3-4	Benzylpenicillin (intravenous) + addition of gentamicin Cefotaxime* + addition of erythromycin	3 gram x 4 5 milligram/kg x 1 1-2 gram x 3 500 milligram x 4	7-10 days

CRB-65; Confusion, respiration, blood pressure and age>65y. * Not included among antibiotics categorized as appropriate, see more details in section 5.2.1.

The pre-intervention audit covered nine months; January 2014-September 2014. The feedback, ultimo September 2014, was provided by a presentation in a meeting at the respiratory medicine department, where we included information on the project, introduced the recommendations in the CPG and the results from the pre-intervention audit, see Appendix G. The pharmacist (JUH) led the meeting, and the head of infectious disease department took active part in discussion and commented on CPG recommendations and audit results. We also distributed the novel pocket version of the national CPG. The post-intervention audit covered six months; October 2014-March 2015.

Patient characteristics in the pre- and post-intervention period where compared using Pearson´s χ^2-analysis for categorical data and Student´s *t* test for continuously data. The effect of the intervention on empirical antibiotics and treatment duration was analysed with segmented time-series regression analysis, using interrupted time series (ITS) design. With ITS design, we evaluate both a level-effect and a slope-effect. Consequently, we estimated the effect of the intervention (both immediate, delayed and sustained effect) while taking into account the time trend (115). The analyses were controlled for autocorrelation and seasonality by applying Durbin-Watson statistics and autocorrelation function plot. Student's *t*-test was used to compare mean changes in empiric antibiotic prescribing and total treatment duration between the pre- and post- intervention period. For dose we applied Pearson´s χ^2-analysis to determine change pre- and post-intervention. A p-value of < 0.05 was considered statistically significant.

3.5 Ethics

For all three studies, The Regional Ethical Committee was contacted, written or verbal, preceding study start. In the first study, based on 2008-data, the Regional Ethical Committee approved the final protocol. For the retrospective patient record study and the intervention study, which was based on 2010 and 2012 and 2014 and 2015-data, respectively, no approval was prerequisite. The Regional Ethical Committee found the two latter studies to be quality improvement initiatives/health-care research with minimal risk for patients. The studies did not include any medical procedures. Data was reported anonymously and confidentially maintained. Written consent was not required. For all three studies the data protection supervisor at UNN approved the final protocols.

4. Results

4.1 Paper I

Høgli JU, Småbrekke L, Garcia BH. *MAT-CAP: a novel medication assessment tool to explore adherence to clinical practice guidelines in community-acquired pneumonia.* Pharmacoepidemiol Drug Saf 2014;9:933-41.

Content validity was demonstrated for 15 QIs, by a panel comprising six experts in treating inpatients with CAP. The QIs covered areas as empirical antibiotic treatment, microbiological diagnostics, pathogen specific treatment, dose adjustment according to renal function, switch from intravenous to oral treatment and treatment duration. The 15 QIs were reformulated into review criteria and included in a MAT-CAP. Overall reliability was excellent with κ-values of 0.88 and 0.95 for inter-observer and intra-observer agreements, respectively. Similarly, exact agreement ranged 58–100% and 83–100%. Overall applicability was 37.2% (range 0-100). Mean time for data extraction into DCF was 17 minutes (range 8-55), and mean application times were 3.1 and 3.8 min for the two observers. Overall adherence to 812 criteria applied was 59% (range 0-100).

We have demonstrated validity and reliability of a 15-criterion MAT-CAP. Applicability was quite low for some specific criteria. The MAT-CAP was able to pinpoint areas with good clinical performance and areas with improvement potentials.

4.2 Paper II

Høgli JU, Garcia BH, Svendsen K, Skogen V, Småbrekke L. *Adherence to guideline for empirical antibiotics is safe and reduces risk of readmission of hospitalised patients with community-acquired pneumonia in Norway.* [Manuscript, submitted June 2015].

Of a total of 3353 patients with ICD-codes for pneumonia, 651patients (19.4%) were included. Mean age in the study population was 72 years (median 77) and 53.5% were men. The prevalence of patients with high risk of mortality (CRB-65 score ≥ 3) was 7.5%. Of included patients, 10.8% were labelled as penicillin-allergic. An aetiological agent was identified in 21% of patients. Mean LOS was 5.2 days, 30-day mortality 6.9% and 30-day readmission rate 14.4%.

Applicability of MAT-CAP criteria ranged from 14.3 to 100% (overall 66.1%), and extent of insufficient data from 0 to 47.2% (overall 9%). Criteria with applicability < 20% and/or proportion of insufficient data > 20% were excluded from the regression analysis. Consequently, we tested association between adherence to CPG and readmission and LOS for the following three criteria; empirical treatment (C2), microbiological sampling (C4) and treatment duration (C7), and for C6 we used intravenous treatment duration as a proxy.

The proportion of empirical antibiotic treatment with benzylpenicillin or phenoxymethylpenicillin in monotherapy, benzylpenicillin and gentamicin in combination, cephalosporins and others was 51.5%, 22.9%, 12.8% and 12.8%, respectively. Eighty-two percent of patients were prescribed empirical antibiotics according to CPG. Of the 18% non-adherent prescribing, cephalosporins, tetracyclines and macrolides was most prevalent Empirical antibiotic treatment was changed within three days in 14.9% of the patients. Adherent empirical prescribing was associated with a reduced 30-day readmission rate (OR 0.5, 95% CI*;* 0.26-0.98). Mean duration of intravenous treatment was 3.7 days, and one day prolonged intravenous duration was associated with a one day prolonged LOS. Mean total treatment duration was 11.6 days, and 41.3% of the patients had a total treatment duration according to CPG.

Our findings support the Norwegian strategy of prescribing narrow-spectrum antibiotics in this patient population. Moreover, our findings demonstrate the importance of CPGs adjusted to local and national level of AMR. We find the extensive use of benzylpenicillin being safe and reducing risk of 30–day readmission in this study population.

4.3 Paper III

Høgli JU, Garcia BH, Skjold F, Skogen V, Småbrekke L. *An audit and feedback intervention study increased appropriate antibiotic prescribing at a Norwegian hospital.* [Manuscript, submitted June 2015].

In the pre-and post-intervention period we included 253 and 155 patients, respectively. Male patients were in majority in both periods and median age was 73 years pre- and post-intervention. Pre- and post-intervention, mean LOS was 5.3 and 5.9 days, 30-day readmission 22.8 and 16.7%, and 30-day mortality 7.1 and 9.0%, respectively. In the post-intervention period we observed a significant reduction in proportion of patients with AECOPD and penicillin allergy, while we in the same period observed a significant increase in proportion of patients with sampled blood cultures and airways (i.e. nasopharynx and expectorate).

Prescribing of appropriate empirical antibiotic of CAP and AECOPD increased from 61.6% to 83.5% ($P<0.001$) from the pre- to post-intervention period. Post-intervention, the ITS-analysis showed a non-significant immediate increase in prescribing of appropriate empirical antibiotics. However, the post-intervention trend significantly increased and six month post-intervention the increased change in level was significant. In antibiotics categorized as appropriate, 90.9% and 82.9% of the treatment in the pre-intervention audit was maintained during first three days and during entire hospital stay, respectively. For both variables the prevalence of change was even lower post-intervention. For details on distribution of the specific antibiotics prescribed for AECOPD and CAP, separately, pre- and post-intervention see Table 7.

Proportion of patients prescribed high-dose benzylpenicillin decreased from 48.8-38.6% ($P=0.125$) from pre- to post-intervention period.

Total treatment duration decreased from 11.2 to 10.4 days ($P=0.015$). The ITS analysis showed a significant immediate reduction in level of mean total treatment duration. However, post-intervention trend significantly increased and six month post-intervention the effect of the intervention was no longer significant.

Table 7: Distribution of specific antibiotics prescribed among patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and community-acquired pneumonia (CAP)

		Pre-intervention		Post-intervention		Diff.[∞]
		n	(%)	n	(%)	
AECOPD	Benzylpenicillin	34	(32.7)	19	(42.2)	+9.5
	Benzylpenicillin + gentamicin	1	(1.0)	0	-	-1.0
	Amoxicillin/Ampicillin	25	(24.0)	20	(44.4)	+20.4
	Cephalosporines	4	(3.8)	0	-	-3.8
	Macrolides and tetracyclines	38	(36.5)	5	(11.1)	-25.4
	Others	2	(1.9)	1	(2.2)	+0.3
CAP	Benzylpenicillin	70	(47.0)	64	(58.2)	+11.2
	Benzylpenicillin + gentamicin	20	(13.4)	25	(22.7)	+9.3
	Amoxicillin/Ampicillin	6	(4.0)	2	(1.8)	-2.2
	Cephalosporines*	37	(24.8)	15	(13.6)	-11.2
	Macrolides and tetracyclines	6	(4.0)	0	-	-4.0
	Others	10	(6.7)	4	(3.6)	-3.1

[∞] Difference In percentage point from pre-to post intervention period. * From 18.6% to 8.8% pre-to post intervention when patients labeled as penicillin allergic are filtered out

The combination of A&F plus distribution of a pocket version of the CPGs resulted in improved and sustained prescribing of appropriate empirical antibiotics. The intervention did not have any obvious negative effects on mortality, readmission and LOS. Our results indicate that a combination of A&F in concert with distribution of written CPGs, may be suitable for some targeted areas such as empirical prescribing. Supplementary prospective interventions are warranted in order to reduce total treatment duration, as well as optimizing dosing of benzylpenicillin in non-severe patients.

5. Discussion

Regarding antibiotic treatment of hospitalized patients with CAP, this thesis shows both areas with high clinical performance and areas with improvement potentials, exemplified with empirical antibiotic treatment and total treatment duration, respectively. In a selected and homogeneous study population, the Norwegian strategy with profound use of benzylpenicillin was found safe and associated with reduced risk of readmission within 30 days. The intervention study with A&F design combined with distribution of written CPG recommendations resulted in a substantial and sustained increase in empirical prescription of appropriate antibiotics. However, for reducing total treatment duration and optimization of dosage of benzylpenicillin in non-severe patients additional prospective interventions should be explored.

5.1 Medication Assessment Tool (Paper I and II)

5.1.1 Validation of MAT-CAP

Validity comprises content validity, feasibility and reliability. In our studies, the validity demonstrates whether the MAT-CAP measurements correctly reflect clinical data, and whether we can trust the results provided by MAT-CAP application.

Content validity

The QIs and review criteria selected for assessing quality of care should ideally be based on scientific evidence linking process of care to clinical outcome (10, 116). By using suboptimal QIs, the improvement in performance may have no valuable effect on quality of care. Consequently, resources used for both measuring and improving these QIs will be wasted (117).

In the local CPG from 2009, the scientific evidence and grading of evidence of the CPG recommendations was not informed. In such circumstances, QIs should be developed alongside consensus methods collecting expert opinion. We applied a modified Delphi technique for collecting consensus, which is a method that is proven effective in other QI-development initiatives (50, 118). Overall six physicians from UNN Tromsø, Harstad and Narvik participated. No guideline exists on number of experts to include in a Delphi

technique, and in literature the range in number of experts is between 4 and 3000 (119, 120). Importantly in our study, the panel was heterogeneous and included both clinical and academic trained physicians. They agreed upon all but one of the QIs, no comments were received concerning missing QIs, and the QIs developed are comparable to other QIs developed for CAP to assess process of care (50). Optionally to Delphi technique, we could have approached content validity with a focus group technique, allowing for more detailed discussion. However, the six included physicians actively commented on our suggested QIs. Furthermore, focus groups are more resource demanding, and can also refrain participants from fronting their opinions as anonymity is lost in face-to-face meetings (111).

Concerning selection of QIs, we acknowledge that dose and vaccination should be covered in future MAT-CAP. For dose, we have only focused on adjustment of dose according to renal function. Vaccination was not a part of the CPG recommendations in the local CPG in 2009, but is included in the current national CPG.

Altogether, as our QIs are based on CPGs, expert opinion and comparable to other QIs for CAP, we argue that content validity is demonstrated for the MAT-CAP and that the QIs reflect essential aspects of quality of antibiotic treatment of inpatients with CAP. Nevertheless, we may potentially challenge the demonstrated content validity for the criterion concerning prescribing of benzylpenicillin in combination with gentamicin. Here we do not separate between non-severely and severely ill patients as recommended in CPG and by the expert panel. This is discussed in detail in section 5.2.1 (see paragraph named “empirical treatment”).

Original and simplified MAT-CAP

Content validity was established for the criteria included in the original MAT-CAP. The simplified MAT-CAP (Paper II) does not differ substantially from the original MAT-CAP (Paper I) with regard to content even though some criteria were merged, some omitted and for some, wordings were changed to enhance comprehensibility and consequently reproducibility.

The criteria to include in the simplified MAT-CAP were carefully selected. From the original 15-item MAT-CAP (Paper I), seven criteria were included in the simplified MAT-CAP (Paper II). Moreover, of these seven criteria, only three criteria could be included in analysis

exploring association between adherence and clinical outcome. Obviously, developing the "perfect" MAT-CAP was challenging. Retrospectively, we acknowledge that some of the criteria in the original MAT-CAP had imprecise formulations or incorrect wordings which impaired interpretation and provided meaningless results. In addition, some of the criteria were superfluous. The process from original to simplified MAT-CAP was a result of merging, omitting and change in wordings of specific criteria, and are described below.

Merged criteria: We merged criteria comprising the same aspect of treatment, i.e. empirical treatment (original no. 2,4 and 5; C2 in the simplified MAT-CAP), pathogen specific treatment (original no. 11 a-e; C5 in simplified MAT-CAP) and total duration of treatment (original no. 15 a-d; C7 in simplified MAT-CAP). Merging of criteria was necessary in order to be in line with study objectives in Paper II. If not merging the criteria, applicability had been low and enabled us from exploring association between adherence and clinical outcome. Overall, merging of criteria seemed to work well.

Omitted criteria: Criterion no 3. in the original MAT-CAP (documented justification for not receiving penicillin) was found to be superfluous as it is covered by criterion no. 2, 4 and 5 (C2). Criterion no. 6 and 7 in original MAT-CAP (prescription of gentamicin only in severe infection) was challenging due to scarce use of CRB-65 as scoring tool among prescribing physicians at UNN. Assessing prescribing based on a tool not applied at time of prescribing is difficult, and also demonstrates the challenge with intention-to-treat in retrospective observational studies. We met this challenge by omitting criterion no. 6 and 7, and categorized all patients prescribed benzylpenicillin in combination with gentamicin as adherent –regardless of severity status (consequently included in C2 in Paper II). More details are given in section 5.2.1 ("empirical treatment"). Criterion no. 10 in the original MAT-CAP (amendment in treatment as a result of microbiological diagnostics) was intended to reflect de-escalation of antibiotic treatment. However, imprecise formulation of the criterion resulted in a meaningless criterion that did not reflect appropriateness of de-escalation. Criterion no. 12 in the original MAT-CAP (dose adjustment in accordance with renal function) was challenging due to the cut-off for impaired renal function was a glomular filtration rate (GFR) of 80 ml/min, i.e. the criterion was applicable to a high proportion of patients. However, for an antibiotic as benzylpenicillin there is no necessity to adjust dose until GFR < 50 ml/min. The criterion gave meaningless results and no information whether dose was appropriate or not. Criterion no. 14 in the original MAT-CAP (choice of oral antibiotic treatment at time of

switch from intravenous formulation) demonstrated acceptable reliability in Paper I. However, as we have few registered broad-spectrum oral antibiotics, selecting the oral antibiotic is not straightforward in cases initially prescribed cephalosporines, and we found the criterion to depend on user`s interpretation (i.e. being implicit) instead of being explicit, which again can influence the level of adherence. We believe that the favourable reliability findings were influenced by high degree of empirical prescribing of benzylpenicillin, which is switched to phenoxymethylpenicillin. Overall, omitting these criteria were necessary and it indicates that the original MAT-CAP had flaws. Overall, it can be questioned whether the process of formulating criteria was optimal.

Change in wordings: In the simplified MAT-CAP, some amendments in wordings specification were done in both the tool itself and in the application guide in order to enhance application and provide meaningful results. To illustrate, for the original MAT-CAP-criterion no. 8 (C3 in simplified MAT-CAP; documented justification when treatment is amended first 48–72 h) we specified and narrowed the definition of "amendment of treatment" before applying it in Paper II. In Paper I switch to oral antibiotics was included in the definition "amendment of treatment". However, as the intention was exploring if amendment was concerning risk of treatment failure, the definition had to be narrowed. Overall, the change in wording seemed to work well as it provided meaningful results in Paper II.

Feasibility

Feasibility comprises applicability of MAT-CAP criteria, quality of data in patient records to apply the MAT-CAP criteria and resources for tool application. Original MAT-CAP (Paper I) had feasibility issues for specific criteria including low applicability or insufficient data to answer the criteria. Overall applicability was low compared to other MATs (57, 59).

Applicability of MAT-CAP criteria

Applicability reflects the proportion of patients for which a specific criterion or the criteria overall is applicable. Total applicability was 37.2% in Paper I and 66.0% in Paper II, where increased applicability in Paper II was mainly a result of merging criteria. In literature, no clear cut-off for acceptable applicability is defined. While some studies have applied < 80% as a definition of poor applicability, others have applied a cut-off threshold of 1% (121, 122). This implies that applicability must be considered based on setting and objective. In Paper I we argued against excluding low-applicability criteria based on MAT-CAP can be applied

prospective as a clinical tool where the criteria can serve as reminders of CPG recommendations in rare clinical situations. In Paper II, where the aim was to test association between adherence and clinical outcome based on retrospective data, criteria with low applicability had to be excluded. Consequently, two criteria with applicability below 20% were excluded from the regression analysis (C3; documented justification when treatment is amended during first 72 hours after initiated empirical treatment and C5; pathogen directed treatment according to guideline).

Despite striving for increased applicability, MAT-CAP is not designed for achieving high overall applicability. To illustrate, applicability of the criterion assessing pathogen directed treatment is influenced by absence of an aetiological diagnosis in up to 50% of CAP-patients.

Data quality in patient records; availability and reliability of data extraction

Patient records are the source for most studies exploring process of care in health care services, although these data is primarily intended for use in the clinical setting and not for research (123). Applying patient record data in research can be challenging due to concerns regarding availability of data as well as reliability of the data extraction process.

Availability of data reflects whether necessary data is present in the patient record (124). Insufficient data can affect judgement on appropriateness of treatment and possible associations with outcome. In the literature, threshold for poor availability of data are in several studies set at 20-25% (50, 121, 125). In Paper I (original MAT-CAP), criterion no. 1 (timing of first dose) and criterion no.14 (timing of switch from intravenous to oral treatment) had insufficient data >20%. However, we did not exclude these criteria due to MAT-CAP can be applied prospective as a clinical tool. Prospective collection of data will probably reduce the challenge with availability or lack of data. Contrary, in Paper II we had to exclude criteria with insufficient data >20%, as appropriateness cannot be assessed and potential associations with clinical outcomes cannot be distinguished. We found a systematic lack of data on; i) timing of first dose of antibiotics (C1), ii) CRB-65, and iii) variables necessary to assess appropriate timing of switch from intravenous to oral antibiotics (C6). For i) we met this challenge by excluding the criterion from our analyses on association with clinical outcomes, for ii) we calculated the CRB-65 score ourselves based on information on time of admission, and for iii) we used length of intravenous antibiotic duration as a proxy for timing of switch.

Data collection procedures needs validation in order establish reliability when different persons extract the same data (information bias) (9). Recently, a master student at UiT has explored the reliability when two persons collected the same data from electronic patient records with inter-rater reliability testing and percent agreement (126). The reliability testing was performed on data extracted from fifteen randomly selected patients included in the study population in Paper II, by applying the DCF shown in Appendix B. Overall, the data collection procedure was found excellent (κ; 0.98 and percent agreement; 93.3%). On variable level, it was mainly the clinical variables blood pressure, heart rate and body temperature that were associated with lower reliability due to difficulties in interpretation of hand-written medication charts and several information sources within the records. For extraction of data on antibiotic prescribing agreement was good, which is reassuring as assessing appropriateness of antibiotic prescribing is the main purpose of a MAT-CAP. Intra-rater testing was not performed, but from own experience with MAT intra-rater reliability testing it is frequently higher compared to inter-rater testing.

Time consume

MAT designers have previously found that time consume is dependent on data collection time, familiarity with the tool, the number of criteria and how fast they can be applied (9, 127). In Paper I, data collection and application time was in line with findings from previous MATs, and is also comparable with the time a clinical pharmacist use when collecting data for medication review (personal opinion) (59, 128). The intention of strict inclusion and exclusion criteria in Paper II was not only to yield a homogenous study population, but was also a result of time constraints (time-consuming manual data collection). During intra-rater test in Paper I, the rater applied MAT-CAP significantly faster the second time compared to the first time nine weeks prior, which supports the familiarity-theory (9, 127).

In a previous MAT, the review criteria were automatically applied on data in electronic patient records (58). In Norway, electronic prescribing and medication charts will be fully implemented in hospitals within few years, which will enable automatic data collection of MAT and other tools. Moreover, it will also allow for built-in decision support for appropriate antibiotic prescribing, use of electronic quality indicators and quality registers.

Reliability

Reliability was tested in Paper I by applying Cohen`s kappa (κ) statistics and percent agreement to express intra- and inter-rater agreement in MAT-CAP application. Cohen's kappa accounts for agreement occurring between the raters due to chance, but an acknowledged problem is a possible low score in cases where expected degree of random agreement is high (111). Therefore, percent agreement should be reported alongside Cohen's kappa. We found reliability of MAT-CAP to be excellent (κ>0.75) both in intra- and inter-rater testing. However, before applying MAT-CAP in Paper II some amendments and specification were done in both the tool itself and in the application guide in order to enhance application and to provide meaningful results (previously described). High reliability has been also been documented in previously MATs, and indicates that this methodology is reliable (57, 59).

5.1.2 Testing association between guideline recommendations and clinical outcome

Frequently, QIs with demonstrated content validity (or criteria in this case) are later found to be unfeasible or unreliable when tested on clinical data, and 50% or more of suggested QIs or criteria are often discarded (129). This demonstrates that content validity alone is insufficient, and that testing on clinical data is vital. Overall, three criteria in the simplified MAT-CAP (Paper II) was found suitable for exploring the association between adherence and clinical outcome. This is comparable with findings from Schouten *et al*, where five out of fifteen QIs developed to assess antibiotic prescribing of CAP and AECOPD in Dutch hospitals were included in further studies (50, 84). Of these five QIs, one QI was associated with clinical benefit for patients (empirical treatment).

Our findings on association between empirical treatment and readmission add value to the validation of the tool, as it demonstrates that MAT-CAP can link process-of-care to clinical outcome. Due to Paper IIs observational design, it is important to highlight that the association between empirical prescribing and readmission is found, but no causal relationship deduced.

5.1.3 Internal and external validity

Internal validity

Selection bias, information bias and observer bias describes internal validity of a tool (130). Our inclusion and exclusion criteria may have introduced selection bias. We have not tested the MAT-CAP on data from patients with more complex disease histories, such as in malignity and immunosuppression. However, there is no discrepancy between CPG recommendations for these patients and the patients included in Paper II, and we therefore hypothesize that the MAT-CAP is valid also in the more heterogeneous study populations Information bias (data extraction from patient records) has been described previously. It was tested and found good. Concerning observer bias, we conclude that a well formulated MAT-criteria and application guide limits ambiguity on application. Further, application time was comparable for two different pharmacists and was reduced with increasing number of applications. A limitation of MAT-CAP, is that reliability has not been tested on different professions, but only on pharmacists familiar with the tool.

External validity

The original and simplified MAT-CAP had impaired external validity. As the local CPG served as template for criteria development, the MAT-CAP could not have been applied in other Norwegian hospitals or in other hospitals abroad without being validated for use in those settings or countries. Recommendations on empirical choice are probably what differ most between settings due to differences in level of AMR and prevalence of common pathogens. For other aspects of treatment, such as treatment duration, European CPGs can be comparable and be based on the same evidence. Previous MATs have demonstrated that a MAT can be adjusted to different settings (and countries) as long as the content are adapted to local and national CPGs (59, 62).

5.1.4 The new MAT-CAP 2014

A master student at UiT have developed an up-dated version, called MAT-CAP 2014, based on the new national CPG (126). However, feasibility limitations such as low applicability (overall 27.5%) and reduced user-friendliness were found also in the new version. MAT as a methodology have several advantages, such as being explicit in nature, possibility to record and report both justified reasons for non-adherence as well as lack of availability of data in patient records, and allowing audit of several aspects of treatment simultaneously. This

enables pin-pointing of areas for improvement. However, we welcome future discussions whether we should continue striving for the optimal MAT-CAP, spend resources keeping it up-to-date, and use resources on manual data collection. For retrospective use we believe MAT-CAPs future is attenuated. In prospective data collection, MAT-CAP based on automatic data collection with build-in systems reporting adherence may serve as a clinical tool for pharmacists and physicians. However, this will require further studies, other methods will perhaps be more feasible for auditing prescribing.

5.1.5 Adherence

Adherence in MAT-methodology

In Paper II, we calculated adherence based on the original formula for MAT, where all Yes-responses are presented as percentage of the sum of Yes+No+Nj+IDs. However, several MAT-developers have questioned this approach for calculating adherence (9, 127). The discussion concerns whether Nj and IDs should be included in the denominator or not. If included, as it currently is, a "worst-case" scenario is presented, meaning that high prevalence of Nj and IDs will produce lower adherence. In Paper II, the criterion concerning pathogen directed treatment (C5) was categorized as intermediate adherence. If Nj had been included in the nominator, counting as adherence, the criterion would have been categorized as high adherence.

Several alternative methods for calculation have been suggested. One alternative is presenting Yes-responses as percentage of the sum of Yes+No, and thereby depicting a "best-case" scenario. Another alternative is presenting No-responses as percentage of the sum of Yes+No+Nj+IDs. Then non-adherence is reported. However, both alternatives require IDs and Nj to be reported alongside. Obviously, the optimal way of calculating and reporting adherence in MAT methodology needs clarification.

Another drawback with MAT is that reporting level of adherence alone is sometimes insufficient because more information about the non-adherence is needed in order to understand it and suggest improvement strategies. E.g. was the length of prescribing too long or too short? Was the dose to low or too high?

Adherence in general

Several studies describing the development and testing of QIs have applied a cut-off where QIs with performance score above 85-90% are excluded (50, 125). The authors argue that if indicator performance is already high, there is little room for improvement. Contrary, others have debated that QIs with low improvement potential is just as important as QIs with high improvement potential; in hospitals with low improvement potential, continuous audit of practice is important to ensure performance is stable at high quality – especially when performance is linked to clinical outcome (as in Paper II for empirical prescribing) (121).
In Paper II, we categorized high, intermediate and low adherence as >75%, 50-75% and <50%, respectively, in line with previous MAT-studies. We have not found any similar categorization of adherence or any consensus on how to categorize adherence when exploring appropriateness of antibiotic prescribing. This specific categorization was mainly descriptive, and was not included into any analysis (i.e. in the regression analysis, prescribing where either "adherent" or "non-adherent"). It is important to recognize that 100% adherence should not be the goal in any study population or setting. Deviation from CPGs is sometimes acceptable as CPG recommendation does not adequately address all patient scenarios (116). Nevertheless, deviations from CPG recommendations should be documented in patient records.

Several studies have assessed and demonstrated the association between a combination of QIs ("bundles") and clinical outcome (131-133). Unfortunately, overall adherence in MAT-methodology cannot be considered as a bundle. The criteria to include in such a bundle must be considered very carefully. In Paper II, a potential "bundle" could be empirical treatment, microbiological diagnostics and total treatment duration, however this needs further clarification.

5.2. Community-acquired pneumonia (Paper II and III)

The focus of this PhD project has been to promote appropriate prescribing of hospitalised patients with CAP. Although we also included AECOPD-patients in Paper III, as CAP and AECOPD are closely related, the main focus of our discussion is CAP and AECOPD will only be discussed shortly in section (5.2.4).

5.2.1 Severity assessment, timing of first dose and empirical antibiotic prescribing

Severity scoring tools to guide empirical treatment in CAP-patients

CRB-65 is validated for predicting severity and risk of mortality (112, 113, 134), but has been criticised for reduced accuracy in elderly, and for not considering social factors and comorbidity. It is also emphasised that severity scoring tools should be regarded as decision support tools to be used alongside clinical judgment (135). Studies have revealed that physicians often overestimate severity, and therefore can tools like CRB-65 be of importance (136). In addition, standardized scoring tools provide the possibility to define and compare populations in research (135).

In both the local 2009-CPG and the national 2013-CPG, CRB-65 score guides the recommendations on empirical antibiotic. Evaluating quality of prescribing based on CRB-65 was nevertheless challenging based on not being documented in patient records. In 910 CAP-patients included in Paper II and III, CRB-65 status at time of hospital admission was documented in patient records in two patients. This is not unique for our study. Severity scoring tools, independent whether it is CRB-65 or other tools, are underutilized (137, 138). In an on-going intervention study including the Norwegian hospitals Haukeland, Stavanger and Haraldsplass, it is also observed that CRB-65 to a great extent is abandoned in clinical practice (personal communication Jannicke S.Wathne, The National Centre for Antibiotic use in Hospital). Application of CRB-65 to guide empirical treatment in the Norwegian hospital setting needs further clarification, including a study examining why physicians choose not to use this tool.

A limitation with our study is that we have not separated between patients admitted to an intensive care unit and those who were not. Such data alongside CRB-65 could strengthen assumptions on severity. In the following sections the discussion is based on the assumption that the majority of included patients are non-severe (indicated by CRB-65 score). The reported clinical outcomes in Paper II and III support these assumptions. However, severity is better assessed in a prospective study.

Timing of first dose

In recent years, the impact of timing of first dose of antibiotic have been debated (116). In US, QIs for CAP is widely applied and timing until first dose of antibiotics has been included in a pay-for-performance strategy (139). Recently, this aspect of treatment have been

reviewed and found to be associated with overuse of antibiotics because prescribing physicians focus on early administration instead of establishing a firm diagnosis (116). In Norway, a time frame for administration of first dose has not been recommended. We included this specific criterion in MAT-CAP by means of exploring this in a Norwegian setting. However, data were unavailable refraining us from assessment of association between timing of first dose and clinical outcome. It is generally recognized that it is mainly severely ill patients that will benefit from early administration (102). In our study population and setting non-severe patients dominated, and we therefore suspect that early administration of first antibiotic dose would have had minor impact on clinical outcome.

Empirical treatment

Several factors will guide empirical treatment, including severity, prediction of most likely pathogen, level of AMR and other patient characteristics like co-morbidity, allergy, intolerance and previous hospitalization (103). The rule of thumb in international guidelines is that *S.pneumoniae* should be covered, independent of CRB-65 level. However, increasing severity of disease may require more use of broad-spectrum antibiotics, as other pathogens are more often involved (140).

Our study is the first from the Norwegian hospital setting to explore (and demonstrate superior findings) association between adherence on empirical antibiotic and clinical outcome for a specific group of inpatients with CAP. In other low-AMR countries, recent findings have revealed non-inferior results for benzylpenicillin as empirical selection compared to other antibiotics (141). In addition, recent data from the Swedish CAP register have shown that benzylpenicillin is superior to other antibiotics with regard to mortality, but the results is only applicable in patients with low risk of mortality (CRB-65 0-1) (48).

Beta-lactam and macrolide combination have been preferred in many countries with high level of AMR, both to expand antibiotic coverage and because of the immunomodulatory effects of macrolides. Recently, Postma and colleagues used cluster-RCT design to demonstrate that beta-lactam monotherapy was non-inferior to strategies consisting of beta-lactam-macrolide combination treatment or fluoroquinolone monotherapy with regard to mortality within 90-days. They concluded that these findings suggested that the widespread international CPG recommendations on adding macrolides should be reconsidered (141).

The major findings in Paper II on empirical antibiotic prescribing were the high adherence to CPG recommendations, in addition to that Norwegian recommendations are safe and associated with reduced risk of readmission. Further, the physicians seem skilled in selecting which patients that will benefit from narrow-spectrum antibiotics. In Paper II, we found that 74.4% of patients were prescribed benzylpenicillin (either in monotherapy or in combination with gentamicin) empirically. In Paper III, post-intervention, the proportion was 78.5%. Two other Norwegian studies have reported that 71% and 73% of hospitalised CAP-patients are prescribed this regime (142, 143). Altogether, extensive empirical prescribing of benzylpenicillin in the Norwegian hospital setting should be the goal in patients with CAP irrespective of hospital due to the following reasons; low level of AMR among common pathogens for CAP (34), *S.pneumoniae* should be covered in all patients independent of severity (140), *H.influenzae* is non-invasive and benzylpenicillin is therefore a safe empirical choice in non-severe patients (140), *M.pneumoniae* is mainly prevalent during outbreaks in cycles of 5-7 years(144), and *Legionella* is mainly linked to infrequent occasional outbreaks or a specific patient context (e.g. travelling abroad) (145).

Due to risk of selection bias, our findings in Paper II cannot be directly extrapolated to CAP-patients presenting with malignity, immunosuppression or frequent readmissions. Ideally, we should have included this patient group in our study and only excluded those with co-infection, aspiration- and nosocomial pneumonia. Interestingly, the patient population in Paper III was more heterogeneous (included patients with immunosuppression and malignity) compared to the study population included in Paper II. However, post-intervention, proportion of prescribed benzylpenicillin, severity and clinical outcomes are comparable in the two studies.

Two deliberations in our studies on empirical antibiotics have been the characterization of gentamicin (Paper I and II) and cefotaxime (Paper III). First, as a consequence of not distinguishing between non-severe and severe infection (as previously described during MAT-CAP discussion), adherence and appropriateness of treatment might be overestimated due to a potential overuse of gentamicin, i.e. some patients with low severity are prescribed gentamicin. Second, in Paper III we chose to characterise cefotaxime (and macrolides) as “inappropriate” despite being aware that in the 2013-national CPG this antibiotic is recommended to certain patients. Theoretically, targeting reduction of cephalosporines could have resulted in underprescribing. However, low severity in our patient population suggested

that cefotaxime was only necessary in a minority of patients. During the feedback session, the head of the infection department highlighted the importance of preferring benzylpenicillin plus gentamicin before cefotaxime, but also emphasised that cefotaxime is an alternative in patients with specific complexities. No obvious negative effect on mortality, LOS and readmission was observed when cefotaxime use was reduced. Reduction in use of cephalosporines was probably compensated with increased gentamicin use. Compared to cephaloporines, gentamicin is found to induce less AMR, easier to administer as it is administered once daily, have a faster bactericide effect and cause less endotoxin release (146). On using one daily dose in a short period of time, the risk of nephrotoxic and ototoxic adverse effects are limited (147). Cephalosporin use (along with ciprofloxacin) is associated with increasing levels of extended-spectrum beta-lactamase producing gram negative bacteria (34). Further, use of these antibiotics can result in co-selection of resistance to aminoglycosides, and threaten the Norwegian strategy with extensive use of benzylpenicillin and gentamicin (148). Overall, we prioritized reducing use of cephalosporines and had no focus on a potential overprescribing of gentamicin. Increasing total use of gentamicin is not found to be linked to emergence of AMR (148).

The proportion of patients with amended empirical antibiotics during first three days has been reported in both Paper II and III. In both Papers we found this comparable to other studies (149), and we found no obvious indication of treatment failure.

Approximately 10-15% of patients are labelled as allergic to penicillin, contrasting the estimated prevalence of 1% (150). Inappropriate penicillin allergy labelling is associated with increased LOS, increased health care costs and unfavourable clinical outcomes as increased risk of admission to intensive-care units and mortality (151). Inappropriate labelling precludes patients from treatment with more narrow-spectrum antibiotics. In literature, several ASPs have addressed this topic and have identified, assessed and acted up-on patients labelled as penicillin allergic. With proper assessment and testing, use of broad-spectrum antibiotics can be significantly decreased (152, 153).

5.2.2 Microbiological diagnostics, aetiology and pathogen directed treatment

Microbiological diagnostics is important in the context of surveillance and for targeting pathogen specific therapy. Several national and international CPGs recommend collecting blood cultures in *all* admitted patients diagnosed with CAP (68, 103, 104). Still, the benefit of

microbiological diagnostics for *non-severe patients* has been debated and has also been found limited (116). A Norwegian study by Buscher *et al.* showed that microbiological testing had minor impact for patients, which was expected based on level of AMR among common CAP-pathogens (142). In USA, requiring blood cultures for all patients have been associated with overuse of antibiotics due to false positive tests (116). Adjustment of antibiotic treatment according to positive blood cultures can also reduce antibiotic use and costs (154). Patient context such as travel history and age may also identify potential aetiology (102). Conflicting evidence of the value of microbiological diagnostics can be a result of bias in patient context (e.g. severity and immune status), study setting and design (observational) (103), which overall reduces the external validity and interpretation of the studies. Weighting between clinical and economic considerations is challenging.

The aetiological agent was established in 21.0 and 39.1% of patients in Paper II and III, respectively. The proportion of nasopharynx and expectorate tests were higher in Paper III compared to Paper II, which is reflected by higher prevalence of positive aetiological agents found in Paper III (i.e. higher prevalence of *H.influenzae*, influenza virus and respiratory viruses). We have not explored whether positive tests had clinical impact, or analysed level of resistance among these pathogens. In two recent published Norwegian studies by Røysted *et.al.* and Holter *et al.*, the aetiological agent was established in 37% and 63% of CAP-patients (99, 143). *S.pneumoniae* was the most prevalent pathogen in both studies with 20 and 30%, *H.influenzae* was identified in 6 and 5% of patients and *Mycoplasma pneumoniae* in 2 and 4% of patients, respectively. Røysted *et al.* highlighted that *Legionella* (6%) might be more prevalent in Norway than previously recognized. However, Holter *et al*. found Legionella in 3% of patients. In our studies *Legionella* was not prevalent at all. Information on severity, was not supplied in the studies by Røysted and Holter. Altogether, the demonstrated prevalence among common pathogens for CAP in Norway seems to support the Norwegian CPG recommendations.

5.2.3 Dose, switch from intravenous to oral antibiotic and treatment duration

Dose

Theoretically, initiatives for reducing inappropriate high dosage can result in reduced selective pressure, which again can reduce emergence of AMR (155). Pharmacokinetic and pharmacodynamic principles guide dosage of antibiotics. Benzylpenicillin possesses time

dependent killing. Time must be above the minimum inhibitory concentration (T>MIC) in about 50% of the dosing interval and peak efficacy is reached at about 5 times above MIC (156). In clinical terms, benzylpenicillin 1.2 g x 4 (low dose) is an effective option in the Norwegian setting where the proportion of susceptible *S.pneumoniae* is high (MIC≤0.06 mg/L) (34). Benzylpenicillin 3.0 g x 4 (high-dose) is recommended in patients with severe infection due to possible altered volume of distribution and protein binding. In Paper III, we managed to reduce use of high-dose benzylpenicillin by 10 percentage points. We suspect that a further reduction is possible based on the majority of patients had a non-severe infection.

H.influenzae is only expected in a minor proportion of patients and rarely results in an invasive infection (140). CPG recommends low-dose benzylpenicillin empirically in non-severe patients with AECOPD and CAP (68, 140). From our point-of-view, the influence of dose (and antibiotic) on clinical outcome in patients with *identified H.influenzae* is not fully established (pathogen-directed treatment). For *H.influenzae,* a clinical breakpoint for benzylpenicillin has not been defined. From time-kill experiments it is suggested that benzylpenicillin 3.0 gram x 4 can be recommended in *H.influenzae* without resistance mechanisms (157). In a Danish study in bacteremia-patients with *H.influenzae* it was demonstrated that cefuroxime or aminopenicillins should be preferred to benzylpenicillin when *H.influenzae* is identified (158). The same study also found that choice of empirical antibiotic (benzylpenicillin in low-dose) was not associated with increased mortality. Altogether, low-dose benzylpenicillin seems to be an appropriate choice as empirical treatment for non-severe patients. However, in case of identified *H.influenzae* a treatment change might be warranted, either in form of increasing dose of benzylpenicillin to 3g x 4 (when susceptible) or change to an alternative antibiotic (inconsistent evidence).

In a Norwegian study by Blix *et al.*, it was demonstrated that prescribed dose of antibiotics in patients with GFR below and above 30ml/min was approximately the same, suggesting a potential for improvement (159). Unfortunately, we could not explore adjustment of dose according to renal function in Paper II. Other ASPs have targeted dosage optimisation for specific nephrotoxic antibiotics such as gentamicin, with positive effect on patient safety and costs (160). However, in the Norwegian hospital setting gentamicin is frequently only administrated once in CAP patients, which reduces risk of adverse effects (147). Consequently, targeting gentamicin in Norwegian intervention studies might not be vital.

Switch from intravenous to oral antibiotics

A meta-analysis showed that switch at day 2-4 to oral antibiotic in clinical stabile patients is associated with reduced LOS, health care costs and adverse effects, without altering treatment effect, number of recurrent infections and mortality (161). Also in severely ill patients switch of treatment seems safe on day 3 of admission (162). Despite clear benefits, studies from the Netherlands have demonstrated that timing of switch on average was inappropriate in about 40% of patients (84, 163). In a Danish study, timing of switch could be improved in 71% of the patients (164). Lack of a clear strategy or clear CPG recommendations on switch is mentioned as important barriers of early switch, in addition to practical considerations (e.g. lack of comparable oral antibiotics), organizational considerations (e.g. weekend, no senior physician available for counselling junior staff, time constraints/forgets reviewing antibiotics) and misconceptions (e.g. intravenous formulation is "safer" than oral formulations and risk of recurrent infections on to early switch) (163, 165, 166).

There is no international consensus on criteria or algorithms for early switch from intravenous to oral antibiotics. However, strategies based on education, algorithms (printed checklist added to medication chart or bedside) and active review of antibiotic treatment on 48-72 hours post admission are described (84, 167, 168).

A mean intravenous duration of 3.7 days may be considered adequate, but a substantial proportion of patients have CAP of low-severity and duration of intravenous antibiotics could probably have been reduced without risk of treatment failure (Paper II). A meta-analysis demonstrated that inpatients with CAP, presenting with a non-severe infection and no sign of impaired intestinal absorption, are candidates for oral treatment on admission (169). In future, appropriate timing of switch should be explored (and targeted) in prospective (intervention) studies.

Total treatment duration

In RCTs, courses as short as 3 days have been found non-inferior to prolonged courses with regard to clinical success, bacterial eradication, adverse drug effects and mortality in patients with mild to moderate-severe patients (170, 171). Moreover, short courses improves patient compliance, reduce costs, overall antibiotic consumption and selection of AMR (172). Historically, length of treatment duration have been guided by; i) clinical diagnosis (i.e. all patients with CAP recommended 10-14 days of treatment), ii) aetiology, or iii) choice of

empirical antibiotic. Recently, patient characteristics have been suggested to guide length of treatment duration (i.e. severity status or clinical response after initiating empirical treatment) (173). Procalcitonin, which is involved in calcium homeostasis, is elevated in bacterial infections. Procalcitonin-based algorithms to guide treatment duration is novel and upcoming (167). In the local 2009-CPG treatment duration was guided by suspected or confirmed aetiology (Paper II). In the national 2013-CPG, treatment duration is guided by severity status and aetiology (Paper III). In both Paper II and Paper III, the study populations were predominated by patients with low CRB-65, questioning the need for prolonged treatment

Mean total treatment duration was 11.6 days in Paper II (adherence 41.3%) and 11.2 days pre-intervention in Paper III (the latter comprise treatment duration for both CAP and AECOPD). This is in line with international literature indicating that 10-14 day regimen is common (173). Total treatment duration should be targeted in future interventions, both nationally and internationally. The studies by Lesprit *et al*, Avdic *et al.* and Murray *et al.* are among few studies that have targeted total treatment duration (174-176). These studies are prospective and multifaceted, and include strategies such as systematic reviews by ASP-teams, automatic stop-dates at time of initiating empirical treatment and educational outreach visits.

5.2.4 Other considerations

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Antibiotic treatment of AECOPD has been a matter of controversy (177). In this study, we did not explore if decision-to-treat algorithms, such as the recommended Anthonisen-criteria, warranted initiating of antibiotics or not (178). Nor did we explore or stratify these patients according to severity. Consequently, some of the empiric antibiotic treatment might theoretically represent overprescribing. For mild and moderate AECOPD a total duration of 5 days have been demonstrated to be sufficient (179).

Surprisingly, above 50% of patients were prescribed oral antibiotics empirically, where doxycycline dominated. Doxycycline has a favorable once daily administration and an immunomodulatory effect. Still, we aimed for replacing doxycycline with more narrow-spectrum antibiotics. A reduction in doxycycline resulted primarily in increased use of amoxicillin/ampicillin, and no effect on measured patient outcome was observed. In theory, it can be questioned whether penicillin (intravenous or oral) would have been a more

convenient antibiotic compared to amoxicillin/ampicillin based on spectrum and risk of adverse effects. Oral empirical treatment suggests possible outpatient care with limited risk for the individual patient and reduced cost on avoiding hospitalization. Obviously, these patients may have other requirements than intravenous administration of antibiotics (e.g. respiratory support or need for observation).

5.2.5 Model selection and outcome measures

Model selection

In the regression analysis predicting effect on LOS and readmission for patients treated according to CPG, choosing a statistical model to minimize bias estimate, is critical. Traditionally, *all* potential confounders are included in the model and adjusted for (180). By applying DAGs we structurally approach the minimal set of covariates to include in the model, and thereby increasing the statistical efficiency (180). The cofounders selected must be linked to both exposure and outcome. For instance, despite length of stay can influence on readmission it will not influence choice of empirical antibiotic in our patient group, and therefore not included. Moreover, by visualizing the model we are transparent on which variables we have included in the model. For some variables, which were measured, it can be debated whether they should have been integrated in the model. Examples of this are antibiotic treatment pre-hospitalization and seasonality. Pre-hospital was not registered with the specific antibiotic used. Most likely, information on which antibiotic is used and for how long, is most important. Obviously, whether this variable should be included can be debated. For season, we have data on which month the patient was admitted. However, a categorical variable based on month is not easy to fit in the model, and we decided against including it. This can also be debated. Overall, we believe that applying DAGs to guide assumptions for the regression models strengthen our statistical analysis and findings.

Outcome measures

Mortality is frequently described as the gold standard for clinical outcome. In Paper II association between adherence and mortality was not analysed due to (expected) low 30-day mortality rate. Longer observational periods can increase number of deaths, and in other studies 90-day mortality have been measured (141). Despite we have not tested the association between adherence and mortality, our finding of 6% mortality is important

indicating that the Norwegian recommendations are safe in this patient group. Mortality rate in our study is comparable to Swedish data (181).

In Paper II, we demonstrate an association between non-adherent antibiotics (predominated by cephalosporines, macrolides and tetracyclines) and readmission. However, we have not collected data on cause of readmission and therefor we can only speculate on possible reasons of this identified association. Possibly, it may be a consequence of unmeasured variables, undiagnosed and untreated infections or adverse effects such as *C.difficile,* among others. Readmission has been debated as an indicator of quality of care due to methodological considerations such as inaccurate data registration, inaccurate definition (i.e. time frame and explicit description of how readmission is counted) and case-mix corrections (182). We have accounted for these pitfalls; first, as the three hospitals included in our study is geographically spread and the only alternative in the respective towns, patient transfer between hospitals is excluded and registration of readmission is accurate. Second, we have explicitly defined readmission as unplanned readmission for any cause within 30-days, and in-hospital mortality is excluded from readmission calculation. Third, we applied DAGs to guide assumption for testing association to readmission. In addition, readmission is reported alongside mortality and LOS to provide a complete picture of quality of care. Rate of readmission was comparable to European data (183).

LOS is associated to factors in the outpatient setting, and comparing studies originating from different countries is challenging. To illustrate, in 2012 the Norwegian Ministry of Health implemented extensive regulation of the coordination between the primary and secondary care allowing earlier patient discharge from hospital (184). In our study this was reflected by lower LOS in 2012 compared to 2010.

Other outcomes, such as economic and microbiological measures, were not assessed in this thesis. Economic measures can be relevant to include to demonstrate the economic impact of the intervention for health care administrators, as the willingness to support such initiatives in future can increase (185). Microbiological measures are an important as it is one of the main objectives of implementing ASP, and should, if possible, be included in future studies.

5.3. Improving appropriate antibiotic prescribing (Paper III)

5.3.1 Experience with Audit and Feedback and longitudinal perspectives

A&F is a design found to be an important part of ASP abroad (186), and testing this design in a Norwegian setting is important. In a Cochrane review the effect of A&F on practice of healthcare professionals and patient outcome was explored. It was demonstrated that A&F is most successful when baseline performance is low, if supervisors or colleagues provide the feedback, the feedback is provided more than once, if feedback is provided written and oral and when explicit targets or action plans are formulated (5). In our study, pre-intervention audit showed that the targeted objectives had potential for improvement, however only the effect on appropriate empirical antibiotic was substantial and sustained. In our study, a pharmacist and a senior infection disease physician provided the feedback. It is possible that the effect on dose and total treatment duration had been sustained if we together with the department physicians had defined explicit targets to reach for, and if the feedback had been provided more frequently and also had been provided in written format. The retrospective A&F design was suitable for empirical prescribing, and the intervention technique have advantages as minor time and resource demanding. Our A&F initiative was retrospective, and we believe a prospective design with direct feedback at patient level is requested and should be tested in future. In other studies, implementing automatic stop dates in medical charts and active use of algorithms with feedback for promoting early switch and shorter treatment duration have been found successful, and should also be tested in the Norwegian setting (87, 174). Academic detailing can also be an alternative. Altogether, initiatives should be multifaceted, multidisciplinary and aim for sustained effects with no negative effect on clinical outcome (78).

5.3.2 Interrupted time series design

Historically RCTs have been acknowledged as the “golden standard” of causal evidence (111). However, a major drawback with RCTs is cost and in some circumstances such design can be unethical. In addition, when performed in one specific hospital, potential contamination to the control group cannot be ruled out (111). An alternative to the normal RCT is the cluster-RCT, which allows for comparing effect of different strategies and minimize risk of contamination to control group. In the Cochrane review on interventions in hospitals by Davey *et al.* it is suggested that cluster-RCT may be suitable for comparing

efficacy of different interventions, but due to its extensive nature it should be directed towards high priority research (69).

ITS is the strongest quasi-experimental design, and is useful when RCTs are unfeasible or unethical (187). ITS is found to have some important advantages which are not found in RCT, CBA or CCT studies; trend in the pre-intervention period is accounted for and sustainment of the effect of the intervention is explored. Further, graphical presentation of results facilitates the interpretation of the effect of the intervention (188).

Threats to internal validity of ITS concerns number of data point pre- and post-intervention, and number of observations in the dependent variable over time. First, sufficient data points before and after the intervention is needed. No guidelines exist, but increasing number of data points and observations are preferred (187). Some studies have recommended 12 data points pre- and post- intervention in order to adequately evaluate seasonality and long-term sustainment of effect (115). In our study, we included 9 and 6 points pre-and post-intervention, respectively. For number of observations there also exist ranging recommendations in literature. While some recommend a minimum of 30, other recommend 100 observations at each data point (115). Increasing number of observations per data point reduce the variance, giving more stable estimates. In average, number of observations per data point in our study was 27. Obviously, there exist some limitation on internal validity in form of number of data points and observations per data point. However, the design seemed sensitive to detect change in level and trend. The alternative in our study was CBA. If CBA design had been applied in our study, we would have been unable revealing the non-sustainable effect on treatment duration.

Bias in form of competing interventions, changes in composition of the study population (selection bias), changes in the outcome measure (instrumentation bias) or sub-optimal analysis of data can also threaten the validity of the study (187). As far as we know, there were no competing interventions. One event that potentially could influenced our results, is the publication of an annual report on antibiotic consumption in March 2014 and 2015. Data from the pre-intervention period do not indicate that publication of this report influenced our results. Regarding selection bias, changes in physicians and patient characteristics should be considered. Junior staff rotates between departments in periods of 4-6 months. Consequently, some that are active during the pre- and post-intervention phase may not have been present at

the feedback session. However, the attendance of seniors at the feedback session was high, and they frequently advice the junior staff on antibiotic prescribing. Further, empirical prescribing can be initiated in the emergency department (ED) prior to admittance to the respiratory medicine department. These physicians were not invited to the feedback session. Still, their prescribing may be reflected by our intervention as the less experienced ED physicians/junior staff frequently seeks counsel from the specialists at the respiratory medicine department prior to prescribing. Concerning instrumentation bias, we used a standardized DCF both pre-and-post intervention and a list with eligible patients were provided by the hospital administration. Inclusion and exclusion was performed by the main researcher, which subjectively assessed exclusion based on suspected or confirmed co-infection, nosocomial and aspiration pneumonia. In theory, subjective assessment might introduce bias. However, we believe this bias is limited. Statistical analysis was performed by the main researcher and a statistician, and data was processed and analysed in accordance to the Cochrane Effective Practice and Organization of Care guideline for ITS design (189).

External validity is threatened by the fact that the intervention was performed at one department and at one hospital. In our study, the group served as their own control. Greater external validity could be achieved if the intervention had been multicentre (190)

6. Conclusion and future perspective

We have developed a novel medication assessment tool to audit antibiotic prescribing of hospitalised patients with community-acquired pneumonia; The MAT-CAP. Content validity was demonstrated and the tool was found reliable. Applying the MAT-CAP, we were able to pinpoint areas with low and high adherence to CPG. Applicability was quite low for some specific criteria, extent of insufficient data in patient records prevented us from answering some criteria and imprecise formulation of criteria could influence on interpretation. The original MAT-CAP was subsequently simplified and three well-functioning criteria could be applied when exploring associations between adherence to CPGs and clinical outcomes. We identified high adherence on empirical antibiotic prescribing, however a potential for reducing intravenous and total treatment duration was observed. We have demonstrated that extensive prescribing of narrow-spectrum antibiotics such as benzylpenicillin is safe and associated with reduced risk of readmission in patients admitted without malignity, immunosuppression and frequent readmission. Our results illustrate the importance of adjusting CPGs to the prevalence of common pathogens and local and national level of AMR. Finally, we have demonstrated that a retrospective A&F intervention combined with distribution of a pocket version of the national CPG led to a substantially improved and sustained empirical prescribing of appropriate antibiotics. However, we also found that such a design was less suitable for reducing total treatment duration and optimization of dosage of benzylpenicillin. In future, prospective interventions are warranted for reducing intravenous and total treatment duration.

Audit and surveillance

Future implementation of electronic prescribing and medication charts may enable both electronic audit and surveillance, and also facilitate interventions to promote antibiotic prescribing. Ideally, national quality registries for infections such as CAP should be developed.

The future of MAT-CAP is uncertain, at least for retrospective use. If the tool can be integrated in the future information technology, allowing for automatic data collection and/or build-in feedback to prescribers on adherence, the future of a MAT-CAP can be more

optimistic. Nevertheless, we believe it is time to focus on other methods for auditing antibiotic treatment.

Community-Acquired Pneumonia

For CAP patients, it is important to ensure extensive use of empirical prescribing with benzylpenicillin also in future, for which audits and interventions are crucial. Furthermore, it is important to explore whether our findings on empirical antibiotic prescribing can be extrapolated to a more heterogeneous study population. In addition, as majority of patients in our study were non-severe patients, it will be valuable to investigate the characteristics of Norwegian CAP-patients with severe infection (CRB-65 3-4 and/or admitted to an intensive care unit) with regard to aetiology and antibiotic treatment, and consequently establish the most appropriate treatment in this specific group. Reducing time of intravenous administration and total treatment duration are two important aspects that should be prioritized in future prospective and multidisciplinary ASP-initiatives. Qualitative studies may provide knowledge about barriers for adhering to CPG recommendations.

Antibiotic stewardship programs

ASPs will most likely be implemented in the majority of Norwegian hospitals the following years. It is important to measure the effect of implementing ASP, including a wide range of outcomes. Generic QIs, such as those developed by van Bosch *et al. (54)*, are interesting and can be useful when evaluating ASP. Further research should focus on identifying the most suitable interventions, taking the settings, objectives, contexts and available resources into account. Multicentre studies should be performed in order to increase external validity, and ITS design should be applied to measure effects of interventions.

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Appendix A

Medication Assessment Tool-calculations

MAT-adherence calculation

$$Adherence = \frac{Yes}{\text{Yes} + \text{No} + \text{Noj} + \text{IDs}}$$

MAT-applicability calculation

$$Applicability = \frac{Yes + No + Noj + IDs}{Sum\ all\ response\ alternatives}$$

Reliability-calculation (1)

To calculate reliability, 6x6 matrices are developed:

	Rater 1						
Rater 2	NA	Yes	No	Noj	IDq	IDs	Total
NA	a_{11}	a_{12}	a_{13}	a_{14}	a_{15}	a_{16}	X1
Yes	b_{21}	b_{22}	b_{23}	b_{24}	b_{25}	b_{26}	X2
No	c_{31}	c_{32}	c_{33}	c_{34}	c_{35}	c_{36}	X3
Noj	d_{41}	d_{42}	d_{43}	d_{44}	d_{45}	d_{46}	X4
IDq	e_{51}	e_{52}	e_{53}	e_{54}	e_{55}	e_{56}	X5
IDs	f_{61}	f_{62}	f_{63}	f_{64}	f_{65}	f_{66}	X6
Total	Z_1	Z_2	Z_3	Z_4	Z_5	Z_6	N

Grey matrices express exact agreement between Rater 1 and Rater 2

Extent of agreement, Po, is calculated by $\frac{\text{exact agreement}}{\text{total}} = \frac{a11+b22+c33+d44+e55+f66}{N}$

Agreement by chance, Pc, is calculated by $\frac{x1z1}{N} + \frac{x2z2}{N} + \frac{x3z3}{N} + \frac{x4z4}{N} + \frac{x5z5}{N} + \frac{x6z6}{N}$

$$Cohen's\ kappa, \kappa = \frac{\text{Po} - \text{Pc}}{1 - \text{Pc}}$$

Percent exact agreement	
>90%	Acceptable
80-90%	Minor corrections needed
<80%	Problematic

Cohens kappa agreement	
>0.75	Excellent
0.6-0.75	Good
0.4-0.6	Satisfactory
<0.4	Poor

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Appendix B

Data Collection Form

Section 1. General information

Part 1 The person collecting data		
Name	☐ June Utnes Høgli ☐	Date: Time:

Part 2 Hospital and department	
☐ Tromsø ☐ Harstad ☐ Narvik	Discharging department/ward:

Section 2. Information on patient

Part 3 Patient data			
Year of birth:		Sex:	☐Male ☐Female
Patient-ID (NPR):		ICD-10 code:	
Date of admission:		Date of discharge:	
Time of admission:		Atypical pathogen suspected	☐Yes ☐No
CRB-65 score registered on admission	☐Yes ☐No Sum (0-4): ☐Calculated	Confusion Respiration ≥ 30/min SBP < 90mmHg el DBP≤60mmHg Age ≥ 65 år	☐Yes ☐No ☐MI ☐Yes ☐No ☐MI ☐Yes ☐No ☐MI ☐Yes ☐No ☐MI
SIRS registered on admission	☐Yes ☐No Sum (0-4): ☐Calculated	Temp > 38 el <36®C HR > 90 RR > 20/min Leucocytes ≥12 el <4x 10^9/L	☐Yes ☐No ☐MI ☐Yes ☐No ☐MI ☐Yes ☐No ☐MI ☐Yes ☐No ☐MI
Penicillin allergy	☐Yes ☐No	Yes - description:	
Other diagnosis	☐COPD ☐DM ☐HF	Smoker	☐Yes ☐No ☐MI ☐Previous smoker
Nursing home resident	☐Yes ☐No		
In-hospital mortality	☐Yes ☐No	30d mortality	☐Yes ☐No
30d readmission	☐Yes ☐No	Prior outpatient AB-use	☐Yes ☐No ☐MI

Section 3. Information on antibiotic treatment

Part 4 - Antibiotics									
Antibiotic treament started (name of department)	**Indication**	**Start date**	**Antibiotic**	**Dose**	**Formulation**	**Dose-interval**	**Stop date + # doses given**	**Comments (including information on length of prescription)**	**Amendment***
	Pneumonia								
	Pneumonia								
	Pneumonia								
	Pneumonia								
	Pneumonia								
	Pneumonia								
	Pneumonia								

Comments:

* Cause of amendment: 1. Good response, 2. Lack of response, 3. Positive microbiological test, 4. Allergy, 5. Discharge, 6. Other, 7. Missing information

Section 4. Lab, clinical and microbiological data

	Lab and clinical data										
		Day 1	**Day 2**	**Day 3**	**At switch**	**Discharge**	**Date leucoc. norm**	**Date CRP norm**	**Date HR norm**	**Date RR norm**	**Date temp norm**
1	S-leucocytes (4-12 x 10^9/L)										
2	CRP (<50 mg/L)										
3	Blood pressure (mmHg)										
4	HR (<90/min)										
5	RR (<20/min)										
6	Body temp (<38/>36®C)										
7	SaO2 (%/l given)										
	Renal function (ml/min)	☐ GFR >50	☐ GFR 10-50	☐ GFR <10			Body weight:				

	Switch from intravenous to oral antibiotic				
		Yes	**No**	**Date**	**Conditions leading to IV antibiotics (answers Yes)**
a	Other i.v. indications present	☐	☐		Undrained abscess/empyema, bacteraemia
b	Oral route compromised?	☐	☐		Patient not able to eat and drink
c	SIRS present (≥ 2 criteria fulfilled?)	☐	☐		Temp ≥38/<36, HR >90, RR > 20, leucocytes >12/< 4

	Pathogen	Culture testing								
		Blood	**Urine**	**Faeces**	**Naso-pharynx**	**Expec-torate**	**Wound**	**Other**	**Suceptibility (S,I,R)**	
	Test taken -no growth									
	Test taken - normal flora									
	Clinical implification (+/-)									
	C. pneumoniae									
	H.influenzae									
	K.pneumoniae									
	MRSA									
	M.pneumoniae									
	Pseudomonas									
	S. pneumoniae									
	S.aureus									
	Other:									

L-PCR	Bordetella pertussis	☐Pos	☐Neg	**Other**	Pneumoniae urine antigen test	☐Pos	☐Neg
	M.pneumoniae	☐Pos	☐Neg		Legionella urine antigen test	☐Pos	☐Neg
	C.pneumoniae	☐Pos	☐Neg		M/C. pneumonia antibody	☐Pos	☐Neg
	Influenza virus A	☐Pos	☐Neg				
	Influenza virus B	☐Pos	☐Neg				
		☐Pos	☐Neg				

Comments:

Appendix C

Simplified MAT-CAP criteria and how they relate to the original MAT-CAP criteria

Simplifying of the original MAT-CAP criteria

No. in original MAT	Original MAT-CAP criteria	Simplifying/adaption	No. in current study
1	Prescription of antibiotic ≤ 4 h after admission	Preserved	C1
2	Empirical treatment with penicillin in monotherapy or in combination with gentamicin	Merged with no. 4 and 5	C2
3	Documented justification for not receiving penicillin	Omitted	
4	Prescription of alternative antibiotic when suspected atypical pathogen	Merged with no. 2 and 5	C2
5	Prescription of alternative antibiotic when documented penicillin allergy	Merged with no. 2 and 4	C2
6	Prescription of gentamicin only when severe infection	Omitted	
7	A severe infection is treated with gentamicin as supplement to penicillin g	Omitted	
8	Documented justification when treatment is amended first 48–72 h	Preserved	C3
9	Microbiological sample ordered	Preserved	C4
10	Amendment in treatment as a result of microbiological diagnostics	Omitted	
11	Pathogen directed treatment	Preserved	C5
12	Dose adjustment in accordance with renal function	Omitted	
13	Timing of switch from intravenous to oral antibiotic	Preserved	C6
14	Choice of antibiotic when switched from intravenous to oral formulation	Omitted	
15	Total duration of treatment	Preserved	C7

Appendix D

Application guide for simplified MAT-CAP criteria

Application guide for MAT-CAP*

1. General instructions

The simplified Medication Assessment Tool for Community-Acquired Pneumonia comprise seven criteria (C1-C7). The criteria are given in the form of two statements where a qualifying statement (**q**) is followed by an audit standard (**s**). Each criterion is evaluated and responded to, based on information recorded in the Data Collection Form (DCF) which is an extraction of relevant data from the patients' medical records. The appropriate responses to the criteria are selected among four main response categories; applicability (NA), adherence (YES), non-adherence (NO) and insufficient data (ID).

Criterion applicability

When applying the MAT-CAP criteria to patient data, the qualifying statement (qualifier) of each criterion needs to be addressed first. The qualifier determines whether the criterion applies to the patient and indicates if the standard can be tested. If the circumstance specified by the qualifier is not present for the patient in question, the criterion is answered by ticking NA (not applicable).

Adherence and non-adherence to guideline standards

If the criterion is applicable, the standard following the qualifier can be tested. The standard is a statement of the guideline recommendation and requires a 'YES' or 'NO' response on the basis of evidence that the standard is being met. If a deviation (no-response) from the guideline standard is justified by a cause documented in the patients' medical records, this is indicated by adding a 'j' (justified) next to the appropriate box (also indicated as 'NOj'). Further information on conditions considered as justified reasons for non-adherence is given in the specific application guide on each criterion below.

Missing information

If sufficient information is missing for the appropriate response to the qualifier or the standard, this is recorded as insufficient data (ID) affecting either the application of the qualifier (IDq) or the standard (IDs). If information is missing on both the qualifier and the standard, the appropriate response is always 'IDq'. Missing information is recorded by ticking the 'ID'-box and indicating which of the statements (q or s) that is affected. A 'q' is written next to the box when data regarding applicability is missing. Similarly, an 's' is denoted when data regarding the standard is missing.

*General introduction based on applciation guide developed by Beate Garcia (Thesis 2012. Permission requested)

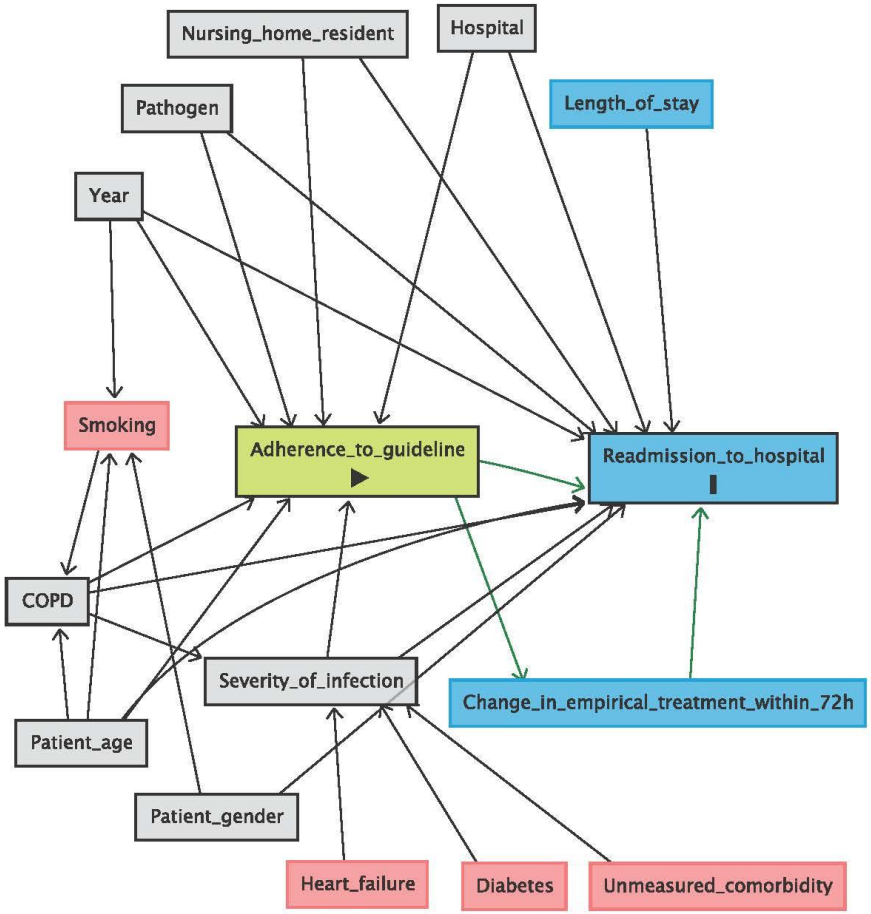
2. Specific instructions for each criterion

No.	Criterion
C1 (Original criterion no. 1)	*The criterion is applicable to all patients and* **NA/ID$_Q$** is not relevant ***Yes*** if an antibiotic is prescribed and administrated within 4 hours after time of admission ***No*** if antibiotic is prescribed and administrated > 4 hours after time of admission ***NO$_j$*** if no due to documented prescriber choice ***ID$_S$*** if time of admission, time for initiating treatment or information regarding prescription is missing
C2 (Original criterion no. 2, 4a +b, 5 a+b)	*The criterion is applicable in all patients.* ***NA/ID$_Q$*** *is not relevant* *Patient presenting without suspected atypical pathogen and penicillin allergy:* ***Yes*** if patient is prescribed penicillin in monotherapy or in combination with gentamicin ***No*** if patient is not prescribed penicillin in monotherapy or in combination with gentamicin ***NO$_j$*** if no due to documented prescriber choice ***ID$_S$*** if information regarding prescription is missing *Patient is presenting with suspected atypical pathogen:* ***Yes*** *If patient is prescribed* ***a)*** *M. or C. pneumonia*; erythromycin, azitromycin, doxycyklin or chlaritromycin **b)** *Legionella:* erythromycin or levofloxacin is prescribed, or if ciprofloxacin is prescribed in severe infected patients ***No*** if patient is not prescribed the AB listed under "Yes" ***NO$_j$*** if no due to documented prescriber choice ***IDq*** if information regarding prescription is missing ***ID$_S$*** is not an option *Patient is presenting with penicillin allergy:* *If applicable, tick off:* ***Yes*** *If patient is prescribed* ***a)*** *Delayed allergy:* cefuroxim, or cefotaxim if CRB-65≥2 **b)** *Immediate allergy:* erythromycin, or clindamycin and gentamicin if CRB-65≥2 ***No*** if patient is not prescribed the AB listed under "Yes" ***NO$_j$*** if no due to documented prescriber choice ***IDq*** if information regarding prescription is missing ***ID$_S$*** is not an option
C3 (Original criterion no. 8)	*The criterion is applicable to patients that have had their empirical AB amended during the first 72 hours after treatment is initiated. Amendment comprise 1) Switch to a new intravenous antibiotic, or 2) addition of a new antibiotic to the current regime* *If applicable, tick off:* ***Yes*** if documented prescriber choice is present ***No*** documented prescriber choice is lacking ***NO$_j$*** is not an option ***IDq*** if information regarding prescription is missing ***ID$_S$*** is not an option. Missing information is regarded as "No"

C4 (Original criterion no. 9)	*The criterion is applicable to all patients and* **NA/ID$_Q$** is not relevant *If applicable, tick off:* ***Yes*** if one or more microbiological tests are sampled ***No*** if no microbiological test is sampled ***NO$_j$*** is no due to documented prescriber choice ***ID$_S$*** is not an option. Missing information is regarded as "No"
C5 (Original criterion no. 11)	*The criterion is divided into a-e, and only one should be applied per patient. If no microbiological test is taken or the tests are negative, the criterion is not applicable* ***Yes*** if positive findings and patient is prescribed: - a) *S.pneumoniae:* benzylpenicillin, phenoxymethylpenicillin + alt. adding gentamicin, - b) *M./C. pneumonia:* erythromycin, doxycyklin, chlaritromycin or azitromycin - c) *Legionella*: erythromycin or levofloxacin, + alt. adding ciprofloxacin in severe patients - d) *H.influenzae*: ampicillin, benzylpenicillin or amoxicillin - e) *S.aureus:* cloxsacillin. ***No*** if patient is not prescribed an antibiotic listed under "Yes" ***NO$_j$*** if no due to - documented prescriber choice - suceptibility findings justifies prescribing optional antibiotic - penicillin allergy ***ID$_S$*** if information regarding prescription is missing
C6 (Original criterion no. 13)	*The criterion is only applicable in patients treated with intravenous antibiotcs and when the four assumptions listed in MAT-CAP are met* *If applicable, tick off:* ***Yes*** if switch is initiated within 24 hours ***No*** if switch is not initiated within 24 hours ***NO$_j$*** if no due to - documented prescriber choice ***IDq*** information to test the four assumptions listed in MAT-CAP is lacking ***ID$_S$*** if information regarding prescription is missing
C7 (Original criterion no. 15**)**	*The criterion is divided into a-d, and only one should be applied per patient. Total treatment duration is calculated based on inhospital treatment + length of prescription at time of discharge. The criterion is not applicable in patients who dies during hospital stay.* ***Yes*** if - a) *S.pneumoniae/H.influenzae;* 7-10 days - b)*M./C. pneumoniae:* 10-14 days - c) *Legionella:* 14-21 days (levofloxacin = 7 days) - d) *S.aureus/gram negative enteric bacilli:*14-21 days ***Nei*** if patient is not prescribed the duration listed under "Yes" ***NO$_j$*** if no due to documented prescriber choice ***ID$_S$*** if information regarding prescription is missing

Appendix E

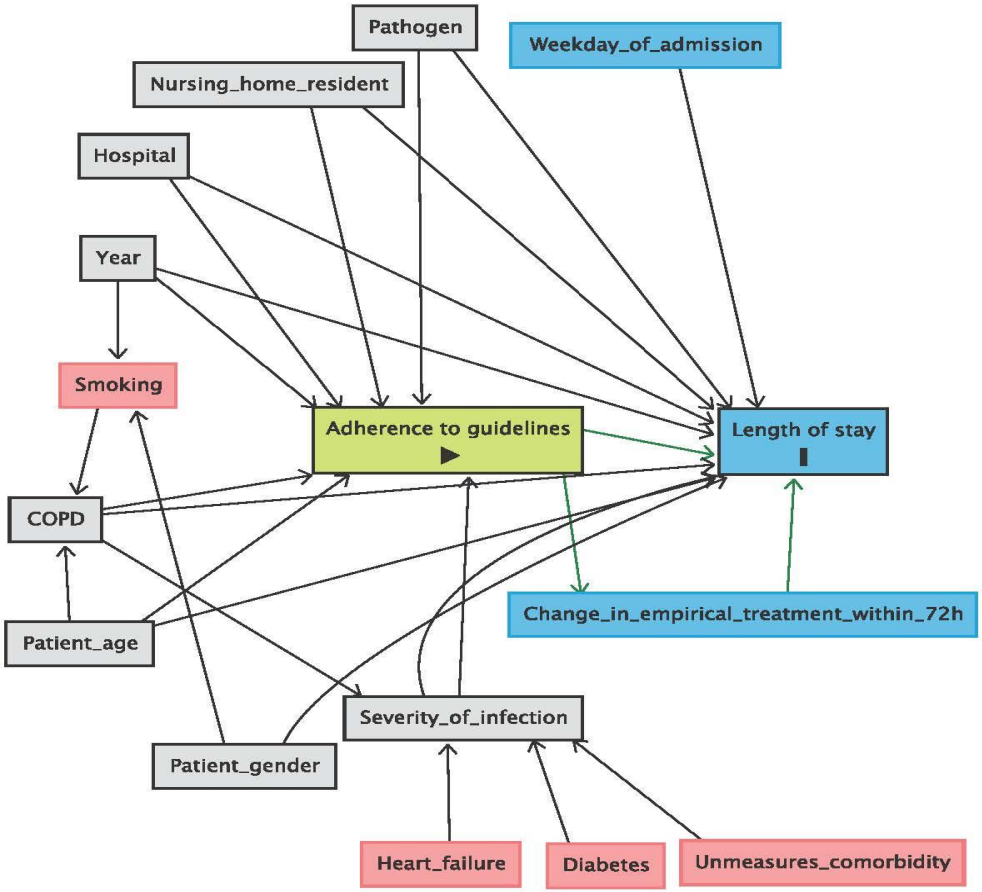
Directed Acyclic Graph; Readmission



To guide assumption and identify covariates to include in the statistical model testing association between adherence guideline (exposure) and readmission (outcome), we applied direct acyclic graph (DAG), here analysed in the browser-based program DAGitty version 2.0. Grey boxes are adjusted variables, blue boxes ancestor of outcome and red boxes ancestor of both exposure and outcome.

Appendix F

Directed Acyclic Graph; Length of hospital stay



To guide assumption and identify covariates to include in the statistical model testing association between adherence to guideline recommendations (exposure) and length of stay (outcome), we applied direct acyclic graph (DAG), here analysed in the browser-based program DAGitty version 2.0. Grey boxes are adjusted variables, blue boxes ancestor of outcome and red boxes ancestor of both exposure and outcome.

Appendix G

Audit and Feedback-presentation (in Norwegian)

Antibiotikabruk på sengepost
Audit med feedback

September 2014

UNIVERSITETSSYKEHUSET NORD-NORGE

Introduksjon

Intervensjonsstudie om antibiotikabruk i sykehus

Mål med studien:

Kartlegge og evt. forbedre etterlevelse av nasjonal retningslinje for antibiotikabruk i spesialisthelsetjenesten, publisert HDir juli 2013

Utarbeidelse av retningslinjen:

- Gi pasienter effektiv behandling
- Minst mulig bivirkninger
- Minst mulig resistens utvikling

=> Rasjonell antibiotikabruk

UNIVERSITETSSYKEHUSET NORD-NORGE

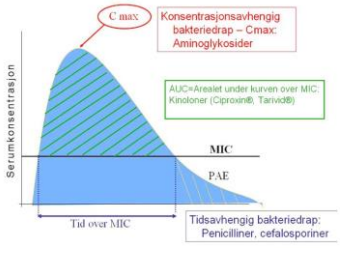
Antibiotikaforskrivning – etterlevelse av retningslinjer KOLS eksaserbasjon og pneumoni

Audit Jan-Sept 2014*	Feedback Sept 2014	Audit Okt 14-Mars 15

• Fokus:
  • Empirisk valg
  • Dose
  • Behandlingstid
	• Er behandlingen i henhold til retningslinjer?
	• Forbedringspotensialer dere vil ta tak i?
		• Skjer det endring i behandlingsmønsteret som følge av feedback?

* Ikke alle pasienter er inkludert per nå.

www.antibiotika.no



KOLS eksaserbasjon

KOLS-eksaserbasjon

Behandling

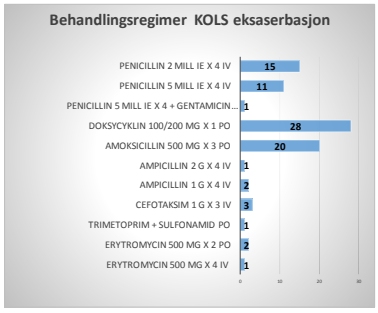
	Medikamenter	Dosering	Varighet	Kommentar
Empirisk standardregime	Benzylpenicillin iv *evt. skifte til* fenoxymetylpenicillin po	1,2 g x 4 1,3 g x 4	5 dager	Ved behandlingssvikt vurderes skifte til cefuroksim iv. Overgang til peroral behandling vanligvis mulig etter 2-3 dager.
Alternativt regime	Ampicillin iv *evt. skifte til* amoksicillin po *eller* amoksicillin/klavulanat po*	1 g x 4 500 mg x 3 500 mg x 2	Til sammen 5 dager	
Penicillin allergi ikke type I Penicillin straksallergi (type I)	Cefuroksim iv Doksycyklin po *eller* Erytromycin iv/po	1,5 g x 3 100 mg x 1 500 mg x 4	5 dager 5 dager 5 dager	

* Amoksicillin/klavulanat forventes registrert i Norge i løpet av 2013. Må søkes registreringsfritak.

Pasientpopulasjon KOLS-ex (n=86)

Alder	Gj.snitt (min,max)	74,3 (44,97)
Kjønn	Menn, n (%)	40 (46,5)
Liggetid (dager)	Gj.snitt (min,max)	5,5 (0,19)
Innlagt fra sykehjem	n (%)	7 (8,1)
Innlagt sykehus siste 30d	n (%)	21 (24,4)
30d mortalitet	n (%)	3 (3,5)
Cave penicillin	n (%)	10 (11,6)

Behandlingsregimer KOLS eksaserbasjon



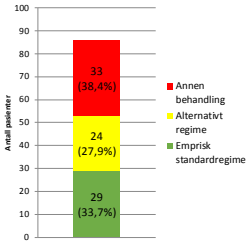
KOLS ex:
Empirisk
Benzylpenicillin 2 mill x 4

Alternativt:
Ampicillin 1 g x 4
Overgang til
Amoxicillin 500 mg x 3 eller
Amoxicillin/klavulanat 500 mg x 2

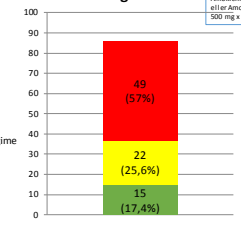
Spørsmål

1. Rasjonale for å velge doksycyklin?
2. Rasjonale for å velge høy dosering av penicillin iv?

Valg av virkestoff ved tentativ diagnose



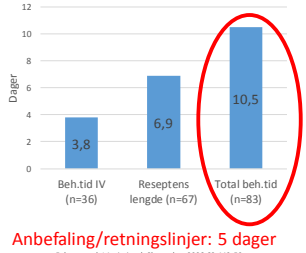
Valg av virkestoff og dose ved tentativ diagnose



KOLS ex:
Empirisk
Benzylpenicillin 2 mill x 4

Alternativt:
Ampicillin 1 g x 4
Overgang til
Amoxicillin 500 mg x 3 eller Amoxicillin/klavulanat 500 mg x 2

Behandlingstid KOLS eksaserbasjon



Anbefaling/retningslinjer: 5 dager

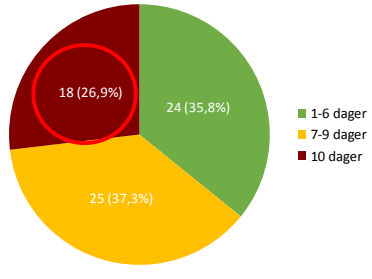
Falagas et al. J Antimicrob Chemother 2008;62:442-50

Spørsmål:

Kan total behandlingstid reduseres?

Hvorfor behandler vi lengre enn anbefalt?

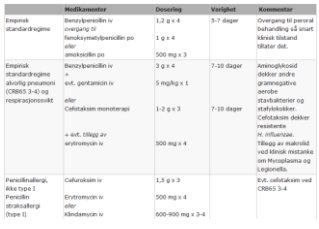
Forskrivningslengde resept (n=67)



Noen punkter dere vil fokusere på i tiden fremover?

Pneumoni

Pneumoni - samfunnservervet



	Medikamenter	Dosering	Varighet	Kommentar
Empirisk standardregime	Benzylpenicillin iv overgang til fenoksymetylpenicillin po eller amoksicillin po	1,2 g x 4 1 g x 4 500 mg x 3	5-7 dager	Overgang til peroral behandling så snart klinisk tilstand tillater det.
Empirisk standardregime alvorlig pneumoni (CRB65 3-4) og respirasjonssvikt	Benzylpenicillin iv + evt. gentamicin iv eller Cefotaksim monoterapi + evt. tillegg av erytromycin iv	3 g x 4 5 mg/kg x 1 1-2 g x 3 500 mg x 4	7-10 dager 7-10 dager	Aminoglykosid dekker andre gramnegative aerobe stavbakterier og stafylokokker. Cefotaksim dekker resistente *H. influenzae*. Tillegg av makrolid ved klinisk mistanke om Mycoplasma og Legionella.
Penicillinallergi, ikke type I Penicillin straksallergi (type I)	Cefuroksim iv Erytromycin iv eller klindamycin iv	1,5 g x 3 500 mg x 4 600-900 mg x 3-4		Evt. cefotaksim ved CRB65 3-4

Gradering av klinisk tilstand?

CRB-65

Symptomer (CRB-65)	Funn	Skår
"Confusion"	Mental konfusjon	1
Respirasjons frekvens	> 30/min	1
Blodtrykk	systolisk <90 eller diastolisk < 60 mm Hg	1
65	Alder > 65 år	1

SIRS

1. Feber > 38°C eller hypotermi < 36°C.
2. Puls > 90/minutt.
3. Respirasjonsfrekvens > 20/minutt eller hypokapni med pCO_2 < 4,3 kPa i blodgass.
4. Leukocytose ≥ 12 x 10^9/L eller leukopeni < 4 x 10^9/L eller > 10% umodne leukocytter.

Sepsis er infeksjon + 2 av 4 SIRS-kriterier oppfylt.
Alvorlig sepsis er sepsis med organsvikt.
Sepsis-indusert hypotensjon er systolisk blodtrykk (SBT) < 90 mmHg, middelarterietrykk (MAP) < 70 mmHg, eller fall i SBT > 40 mmgHg fra utgangstrykk.

Barlow et al. Thorax 2007;62:253–259.

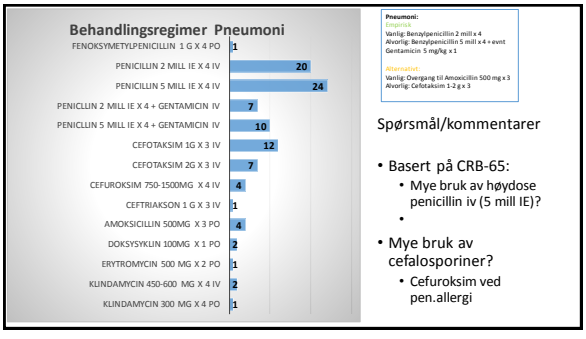
Gradering av klinisk tilstand/alvorlighetsgrad

CRB-65 score	N (%)	SIRS score	N (%)
0	20 (21,1)	0	8 (8,4)
1	37(38,9)	1	16 (16,8)
2	29 (30,5)	2	249(30,5)
3	3 (3)	3-4	37 (38,9)
MD	6 (6,3)	MD	5 (5,3)

		SIRS				
		0	**1**	**2**	**3**	**4**
CRB-65	**0**	5	5	4	4	2
	1	1	5	14	13	4
	2	2	5	10	8	3
	3	0	1	1	1	0

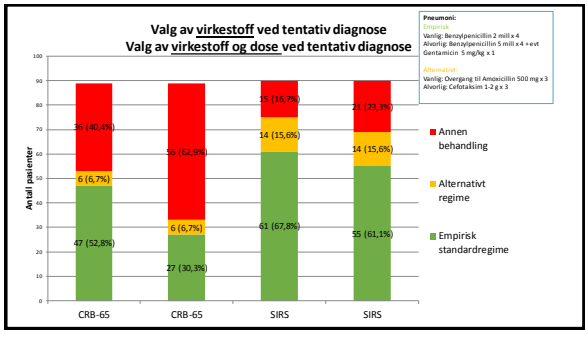
Implementere CRB-65 ved UNN?

Pasientpopulasjon CAP (n=95)		
Alder	Gj.snitt (min, max)	65,9 (19,93)
Kjønn	Menn, n (%)	46 (48,4)
Liggetid (dager)	Gj.snitt (min, max)	5,2 (1,22)
Innlagt sykehus siste 30d	n (%)	19 (20)
30d mortalitet	n (%)	6 (6,3)
CAVE Penicillin	n (%)	14 (14,7)
KOLS	n (%)	24 (25,3)
Immunsuppresiv	n (%)	26 (27,4)

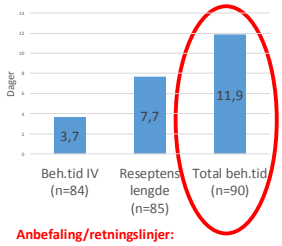


Spørsmål/kommentarer

- Basert på CRB-65:
  - Mye bruk av høydose penicillin iv (5 mill IE)?
  -
- Mye bruk av cefalosporiner?
  - Cefuroksim ved pen.allergi



Behandlingstid Pneumoni



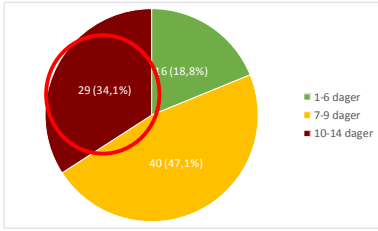
Anbefaling/retningslinjer:
Vanlig pneumoni 5-7 dager
Alvorlig pneumoni 7-10 dager

Spørsmål:

Kan total behandlingstid reduseres?

Hvorfor behandler vi lengre enn anbefalt?

Forskrivningslengde resept (n=85)



Noen punkter dere vil fokusere på i tiden fremover?

Kortversjon i lommeformat