Delayed prescribing –
a feasible strategy to lower antibiotic use for respiratory tract infections in primary care?

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Abbrevations

CME	Continous medical education
EMR	Electronic medical record
GP	General practitioner
ICPC-2	International Classification of Primary Care, version 2
NorPD	The Norwegian prescription database
RCT	Randomised controlled trial
A/L/U RTI	Acute/Lower/Upper Respiratory tract infection
Rx-PAD	a) Prescription peer academic detailing. Refers to the study.
	b) Prescription peer academic detailer. Refers to the tutor carrying out the group-based intervention in the Rx-PAD study.

Summary

Widespread use of antibiotics leads to development of antimicrobial resistance, an increasing threat to health worldwide. The strategy of delayed antibiotic prescribing reduces antibiotics use for respiratory tract infections (RTIs) in experimental settings. The overall aim of this thesis is to explore delayed antibiotic prescribing and its potential in reducing antibiotic use for RTIs in routine primary care.

In a Norwegian primary care setting, we did 1) a controlled trial among GPs on the antibiotics saving effect of recommending delayed prescribing through lectures/group discussion and through a computerised pop-up reminder, 2) a qualitative study among GPs, and 3) a questionnaire study among GPs issuing and patients receiving delayed prescriptions.

We found that GPs regard delayed prescribing as an acceptable strategy for reserving antibiotics to the cases where it turns out to be medically indicated, especially acute otitis and acute sinusitis. GPs have strict requirements as to which patients, for which diagnoses and in which situations they will issue delayed prescriptions, resulting in an infrequent use of the strategy. GPs who received the interventions issued 11% of the antibiotic prescriptions as delayed prescriptions, and 59% of these were dispensed from pharmacies. The interventions gave a statistically significant but clinically modest decrease (RR 0.97) in dispensed antibiotics, without any accompanying increase in prescribed antibiotics.

The use of delayed prescribing should be encouraged as a tool to adhere to treatment guidelines, especially in cases of acute otitis and acute sinusitis. Interventions to promote its use have little effect, and pop-up reminders are not to recommend as a sole intervention, but should be considered as part of multi-faceted interventions. Delayed prescribing's potential in reducing antibiotic use seems to be low in our setting, presumably because of relatively low antibiotic prescribing rates and low patient expectation for antibiotics. The strategy's potential should be assessed in advance of interventions to implement its use. Further research should focus on the clinical outcomes of delayed prescribing for acute sinusitis, and the effect of other intervention elements in the implementation of delayed prescribing.

Norsk sammendrag (Summary in Norwegian)

Utbredt antibiotikabruk fører til antibiotikaresistens, som er en økende helsetrussel over hele verden. I eksperimentelle studier medfører forskrivning av vent-og-se-resept redusert antibiotikabruk ved luftveisinfeksjoner. Det overordnede målet med denne avhandlingen er å utforske vent-og-se-resept-strategien og dens evne til å redusere antibiotikabruken ved luftveisinfeksjoner i allmennpraksis.

Vi gjennomførte tre studier i norsk allmennpraksis: 1) en kontrollert studie av den antibiotikasparende effekten av å anbefale vent-og-se-resept for allmennleger gjennom forelesning/gruppediskusjon og gjennom en pop-up-påminner på legens dataskjerm, 2) en kvalitativ undersøkelse blant allmennleger, og 3) en spørreskjemaundersøkelse blant allmennleger og pasienter.

Vi fant at allmennlegene ser på vent-og-se-resept som en akseptabel strategi for å forbeholde antibiotika til de tilfeller der det viser seg å bli medisinsk indisert, spesielt ved akutt mellomørebetennelse og akutt bihulebetennelse. Allmennleger har strenge krav til hvilke pasienter, ved hvilke diagnoser og i hvilke situasjoner de vil gi vent-og-se-resept, noe som resulterer i at strategien sjelden brukes. Legene som mottok begge intervensjonene gav 11% av antibiotikareseptene som vent-og-se-resept, og 59% av disse ble uthentet fra apotek. Intervensjonene gav en statistisk signifikant, men klinisk beskjeden reduksjon (RR 0,97) i utlevert antibiotika, uten noen medfølgende økning i forskrevet antibiotika.

Bruk av vent-og-se-resept bør anbefales som et hjelpemiddel til å følge behandlingsretningslinjene, spesielt ved mellomørebetennelse og bihulebetennelse. Våre tiltak for å øke bruken av vent-og-se-resept har sparsom effekt. En pop-up-påminner anbefales ikke brukt alene, men bør inkluderes i sammensatte kvalitetsforbedringsprosjekter. Vent-og-se-strategiens antibiotikasparende potensial synes å være lav i vår sammenheng, antagelig på grunn av den relativt lave forskrivningsraten og pasientenes lave forventning om å få antibiotika i Norge. Strategiens potensial bør vurderes i forkant av tiltak for å øke bruken av den. Videre forskning bør fokusere på klinisk utfall av vent-og-se-resept ved akutt bihulebetennelse, og på effekten av andre tiltak for å øke bruken av vent-og-se-resept.

Introduction

Penicillin was discovered by Alexander Fleming in 1928, and made available for patients during The second world war. It was the first really effective medical treatment for bacterial infections, and marked the transition to a new era in medicine – an era characterised by powerful and effective chemicals. Penicillin was nicknamed "the magic bullet", and it made people believe that the fight aginst infectious diseases was won once and for all (1).

However, already in his Nobel Lecture in 1945, Alexander Fleming said: "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe." (2)

Evidently the fight aginst infectious diseases is not won, partly because of antimicrobial resistance, caused by the ecological side effects of the magic bullet itself. Even though Flemings moral – "If you use penicillin, use enough" (2) – may not be directly applicable in our context, he foresaw some major problems in the times to come: patients preference for antibiotics, widespread and "ignorant" use of antibiotics, treatment failure due to resistance, and the moral dilemma of using up the effect of antibiotics on minor illnesses at the expence of severe illnesses.

In our time, Flemings conclusion could be rewritten: "If you use penicillin, you are presumably in Scandinavia". Due to the relatively low levels of antibiotic resistance, old-fashioned phenoxymethylpenicillin is still the most used antibiotic in primary care in the three Scandinavian countries(3, 4). An overall aim must be to maintain the low levels of resistance, through a responsible and sustainable use of antibiotics.

For antibiotics to cause an ecological – and therapeutical – effect, a chain of events must occur. In the primary care setting, the typical chain is as follows: a person must have some sort of complaint, the person must choose to see a doctor for this complaint, the doctor must choose to give a prescription for an antibiotic, which the person must choose to pick up at a pharmacy, and finally, choose to consume. The chain may be broken or modified at all the stages; eg immunisation may alter the incidence of infectious diseases, public campaigns may alter peoples health seeking behaviour, educational interventions may influence on the doctors prescribing habits, and last but not least – efforts may affect whether the patient fills the prescription and/or consumes the antibiotics. This thesis will explore the strategy of delayed prescribing, and its ability to modify this last event in the chain.

Antimicrobial resistance

Antimicrobial resistance is the ability of a microorganism to resist the action of an antimicrobial agent. In clinical medicine, the most common and worrisom form of antimicrobial resistance is antibiotic resistance; bacteria resistant to the action of an antibiotic. The resistance may be natural, as with bacteria naturally lacking the specific molecules attacked by certain antibiotics, or acquired, through the processes of adaptation by genetic change. In the presence of an antibiotic, resistant bacteria will grow and multiply, while susceptible bacteria will be killed. Resistance genes transfer to the offspring and may also spread to other bacteria species. The emergence of antibacterial resistance is a natural consequense of exposing bacteria to an antibiotic environment.

The challenge of antimicrobial resistance is increasing worldwide. The European Centre for Disease Prevention and Control points especially at the increasing trend of combined resistance to several antimicrobials in Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumoniae, and the high levels of meticillin-resistant Staphylococcus aureus (MRSA) (5).

The levels of antimicrobial resistance are considerably lower in Norway compared to most other European countries (6). While the rate of invasive Staphylococcus aureus-isolates with resistance to meticillin in 2011 were above 25% in

Portugal, Italy and Greece, and between 10% and 25% in most other European countries, the rate in Norway and Sweden was below 1%. Although antimicrobial resistance is still regarded a limited problem in Norway (7), the problem is increasing. For instance, the number of MRSA infections, the levels of ESBL producing E. coli and Klebsiella spp. and the level of beta-lactamase producing H. influenza are rising.

Antimicrobial resistance leads to suffering, prolonged illness, higher healthcare expenditures and death. An estimated 25.000 annual deaths in Europe are said to be caused by multiresistant infections (8).

The relationship between the use of antimicrobial agents and the appearance of antimicrobial resistance is well established through observational studies. Areas with high consumption of antibiotics also have high levels of antibiotic resistance (9), and a decrease in antibiotic consumption leads to lower levels of resistance (10, 11). Randomised controlled trials have proven this relationship to be causal at both the individual (12, 13) and the community (14) level.

In the first half century of the antibiotic era, several new types of antibiotics were discovered. Thus, if one type of antibiotics did not work, there was always a new type that would. However, the development of new antimicrobial agents is declining (15). Modern strategies to discover new antibiotics have not succeeded (16), and since 1987 no antibiotics with new modes of action have been found (17). In this situation, the two major strategies to withstand the challenges of antimicrobial resistance are: 1) Minimising the use of antibiotics. 2) Hygienic actions against spread of resistant bacteria.

However, the overall trend is an increased use of antibiotics, both globally and in Norway. European outpatient antibiotic use increased by 0,05 defined daily doses pr 1000 inhabitants pr day (DID) quarterly from 1997 to 2009 (3). In Norway, there was a 16% increase in total sales of antibiotics in humans, defined as DID (excluded methenamine) from 2004 to 2011 (7).

Antibiotics for RTIs in primary care

In the early days of the antibiotic era, the medication was used to heal life threatening infections. Antibiotics soon won large popularity both among doctors and patients,

and the indication for use was extended (1). Today, antibiotics are most often used to shorten and relieve symptoms of mild and self-limiting respiratory tract infections (RTIs). In Norway, 84% of the total human sales of antibacterials in 2011 were used outside institutions, mainly prescribed by general practitioners (7). Straand et al. found that respiratory tract infections represented more than half of the prescribed antibiotics in Norwegian general practice (18). Similar numbers are found in the UK (19). In a recent study from Norwegian primary care (20), Gjelstad et al. demonstrated that 60% of patients who consulted their general practitioner for bronchitis were prescribed antibiotics. The corresponding rate for sinusitis was 74%. Alltogether, antibiotics were prescribed in one third of the RTI episodes. An European observational study, collecting data from general practice in 13 countries, found a 53% antibiotic prescription rate for bronchitis/acute cough (21).

This level of antibiotic prescribing contrasts the evidence from meta-analyses that antibiotics give only a modest, if any, benefit in most respiratory tract infections. In acute bronchitis, a Cochrane review found that the benefit of antibiotics is half a day shortening of cough (22). The reviewers conclude that the magnitude of benefit is similar to that of the detriment from potential adverse effects. In acute sinusitis, a Cochrane review states that 80% of patients given placebo improve within two weeks, compared to 90% in the antibiotics groups. The authors guide clinicians to weigh the small benefits of antibiotics with the potential for adverse effects. For the common cold or purulent rhinitis, there is no benefit of antibiotics (23). Among children with acute otitis media, 15 patients must be treated with antibiotics to prevent one child from having some pain after two days (24). Again, the reviewers state that the small benefit provided by antibiotics must be weighed against the possible adverse reactions.

There are wide variations in antibiotics prescribing rates both between individual GPs and between countries. Gjelstad et al (25) found that among Norwegian general practitioners, the quintile of GPs with the highest antibiotics prescription rate for RTIs prescribed antibiotics three times as frequently as the quintile with the lowest prescription rate. Goossens et al (9) have demonstrated that within Europe, outpatient antibiotic use is three times higher in the highest consuming country compared to the lowest consuming country.

These factors establish the fact that a vast number of primary care patients with respiratory tract infections receive and consume antibiotics without any substantial benefit from it. Allthough the classes of antibiotics most commonly prescribed for RTIs in primary care are not the worst in promoting resistent bacteria strains, the large volume of antibiotics consumed makes this area a strong driving force for bacterial resistance (19). Hence, RTIs in primary health care is a prioritised area when trying to reduce antibiotics consumption.

Using antibiotics for conditions in which it has only marginal or no clinical effect has been labelled *unnecessary* or *inappropriate* antibiotic use or antibiotic *overuse* or *misuse* (19), and the conditions in question have been labelled *self-limiting* (26).

However, at the individual patient level, the question of whether an antibiotic for a mild RTI is necessary and appropriate may not be clear cut. The decision involves balancing different aspects of a situation, and may be elucidated by referring to ethical principles. Beauchamp and Childress (27) pinpoint four main principles within medical ethics, all of them relevant in the decision whether to prescribe antibiotics for RTIs; autonomy, non-malificience, beneficence and justice. The RTI patient may demand a certain treatment, and his or her *autonomy* should be respected. However, unneccessarry treatment with a potent drug that has both individual and societal side effects is *malificient*. Still, the patient might have a chance, though small, that antibiotics may shorten the illness or prevent complications, hence be *beneficial* to the patient. If this is true, then one has to weigh the *justice* in a benefit for this patient towards an increased risk of infections caused by resistant bacteria in another patient, like the case of Flemings mr. and mrs X.

Hence, when a GP prescribes antibiotics for a patient with a RTI, he or she most likely find it necessary at some level. In a recent systematic review of qualitative research on GPs' views and experiences of antibiotic prescribing, Tonkin-Crine et al (28) found that GPs were most satisfied with their prescribing decision if the different influencing factors, e.g. guidelines and patient's wishes, were in agreement. Still, GPs might choose to give priority to patients' wishes over guideline advice, and feel satisfied after having made this choice. The authors state that "…satisfaction with a decision does not necessarily relate to whether or not a decision is appropriate, but

whether the GP believes it is appropriate." Through qualitative research, GPs' reasons for prescribing antibiotics for RTIs has been explored. Petursson (29) found that GPs in Iceland listed several reasons for so-called non-pharmacological prescribing; Physician's insecurity, uncertainty or anxiety, pressure from patients and their families, work pressure and fatigue, the physician's personal character, and organisational factors. The author conclude that when practicing the three objectives of medicine – to cure, to relieve suffering, and to provide comfort – a biomedically inappropriate prescription still may be medically rational in the process of winning the patient's confidence and trust.

Hence, being aware of the lacking or modest effect of antibiotics for RTIs does not necessarily prevent GPs from prescribing. The different reasons for non-pharmacological antibiotic prescribing may roughly be divided into two factors (30): 1) Patient related factors, such as expectations for antibiotics, and 2) Prognostic uncertainty. A tool or strategy that might help GPs in the decision whether to prescribe, resulting in less antibiotics consumption, should preferrably address both these factors. One such strategy is delayed prescribing.

Delayed prescribing

Definition

Delayed prescribing refers to a strategy in which patients are given access to a prescription for antibiotics together with an advice to wait for a certain amount of time before deciding whether to start on the antibiotics or not. The prescribing doctor may explain more or less thoroughly the criteria that should govern the patient's decision, most commonly to start if the symptoms persist or deteriorates. The patient may get the prescription at the first visit, or be asked to come back to the doctor's office and pick it up. The strategy is advocated and studied in cases of potentially self limiting infections, most commonly respiratory tract infections. It may be seen as a middle ground between prescribing an antibiotic to be taken immediately, and no antibiotics prescribing – leaving the patient to re-consult if needed.

The strategy is most commonly referred to as "delayed prescribing", but various other terms have been used, partly reflecting the different views on and explanations

for the strategy; "wait-and-see-prescription" (31), "deferred prescribing" (32), "back-up antibiotic prescription" (33, 34), "back-pocket prescription" (35), "as-needed antibiotic prescription" (36, 37), and "safety-net antibiotic prescription" (38, 39). The terms watchful waiting and active expectancy may include delayed prescribing, but is a broader term of active follow up after (usually) an initial no-treatment consultation. GPs may have their own concepts of the strategy, such as "Friday prescriptions" (40), reflecting the notion of professor Bruce Arroll that "…physicians have spontaneously and independently generated the practice of delayed prescribing." (41) The first notion of the concept in Norwegian medical literature was in an editorial on childhood acute otitis media in Tidsskrift for Den norske legeforening in 2002 (42).

The delayed prescribing strategy is a primary care strategy; it is based on empirical treatment where the etiology of the infection is unknown. Also, the strategy depends on a consultation visits setting, as opposed to a hospital setting. The research on delayed prescribing mostly comes from general practice research institutions in countries with a strong and well developed primary health care service (43), with the exception that much research on delayed prescribing for acute otitis media is done in a pediatric setting.

Delayed prescribing requires that the prescribing GP permits the patient to decide whether or not to consume the antibiotics. Three broad models of decision-making in the clinical encounter have been described (44, 45): 1) The paternalistic model, in which the doctor decides what he thinks is best for the patient, without eliciting the patient's preferences. 2) The informed choice model, in which the patient is informed about the choices she/he has to make her/himself. 3) The shared decision-making model, in which both patient and doctor contribute to the final decision. Delayed prescribing may fit into both the two last models. The strategy has been associated with the shared decision-making model (46, 47), however, delayed prescribing is a clinical tool rather than a communication method, and it has been warned that delayed prescribing should not substitute shared decision-making (48).

Efficacy in clinical trials

In 1997, the first randomised, controlled trial on delayed prescribing was conducted,

to evaluate the safety of the strategy. Little et al (49) evaluated three prescribing strategies in managing sore throat; antibiotics to be taken immediately, no antibiotics, and delayed antibiotics to be taken if the symptoms were not starting to settle after three days. Except duration of fever, they found no significant group differences in illness duration, days off work or school, or proportion of patients satisfied. In the immediate antibiotics group, 99% of the patients used antibiotics, compared to 13% in the no antibiotics group and 31% in the delayed antibiotics group.

Later, similar trials have been conducted on patients with other respiratory tract infections, summarised in a Cochrane review (43). Two trials on lower respiratory tract infections/cough (50, 51) found no clinical difference in patients given delayed or immediate antibiotics. Antibiotics were used by 20% (51) – 45% (50) of the patients in the delayed prescribing group. Arroll et al evaluated delayed prescribing in the common cold (41), finding no difference in symptom score between delayed and immediate antibiotics. In the delayed prescription group, 48% reported to consume antibiotics, compared to 89% in the immediate prescription group. In three trials on childhood acute otitis media (31, 52, 53), the delayed prescriptions were used by 24% (53) – 38% (31, 52) of the patients, compared to 87% of the patients in the immediate antibiotics group (31, 53). Two of the studies compared delayed prescribing with immediate prescribing, the third compared delayed prescribing with no initial prescribing. Among the first two studies, Little et al (53) found more severe symptoms at day three in the delayed prescribing group but no significant differences at day seven, while Spiro et al (31) found no significant difference in symptoms between the two groups.

Adverse effects were similar in both the immediate, delayed and no antibiotics groups, except for a small reduction in diarrhoea in the delayed antibiotics groups for children with acute otitis media (43).

To our knowledge, the clinical outcomes of delayed prescribing for acute sinusitis has not been evaluated in randomised, controlled trials. A questionnaire study (34) concluded that delayed prescribing has the potential to reduce antibiotic use also for this condition.

Most of the RCTs on delayed prescribing also evaluated patients' satisfaction

with the different prescribing strategies. Overall, 87% of the participants in the delayed antibiotics groups were satisfied, compared to 92% in the immediate antibiotics groups and 83% in the no antibiotics groups.

Delayed prescribing may reduce patients belief in the necessity of antibiotics for RTIs, reducing patients consultation rate for similar symptoms in the future . The Cochrane review states that patients intention to re-consult is lower when receiving a delayed prescription rather than immediate antibiotics, but finds no reduced re-consultation rate in the delayed prescribing groups. However, a study focusing on re-consultation rates (54) found that patients more often re-consulted with sore throat if earlier given immediate antibiotics rather than delayed or no antibiotics. The re-consultation rate was lower, though insignificantly, in the delayed compared to the no antibiotics group. Similar results were found in a study on re-consultations for lower RTI (55).

The trials on delayed prescribing have used different ways of delaying; either the prescription has been kept at the reception to be picked up, or it has been issued to patients during the consultation, with instructions to delay. The first method resulted in a significantly lower pick-up rate of 28% compared to 40% using the second method (43). This indicates that the effort required to obtain antibiotics strongly influences the patients' behaviour. Postdating the delayed prescription, i.e. dating the prescription two days later than the date of the consultation so that the patient, in theory, will be unable to use it immediately, does not seem to influence on dispensing rate (56).

Overall, the efficacy of delayed prescribing, in terms of decreased antibiotics consumption, is well proven and would be clinically significant if transferred to daily clinical practice. The patient safety and satisfaction are in line with immediate antibiotics.

Effectiveness in routine care

Although the efficacy of delayed prescribing is well proven in clinical trials, the effectiveness concerning diminished antibiotics use in routine care is not sufficiently explored.

It has been suggested that the first trial on delayed prescribing as an antibiotics saving strategy in 1997 had great impact on British GPs, explaining the increasing difference between prescribed and dispensed antibiotics for children in England in the years following 1997 (57). Compared to the 1993 level, by 2003 prescribed antibiotics had fallen by 37%, while dispensed antibiotics fell by 47%. This equals that 16% of the antibiotics prescriptions for children in 2003 were not dispensed at pharmacies. In 1997, a British practice changed their management policy of childhood otitis media, from routine antibiotics prescribing to delayed prescribing, resulting in a decreased antibiotics use for all childhood infections by one fifth (58). The effect of the changed policy sustained (59). However, in two qualitative studies on delayed prescribing in Britain (60, 61), GPs inform that although delayed prescribing is well known, they seldom use the strategy. In a British survey by Edwards et al (32), about 10 % of patients presenting with RTIs were issued a delayed prescription. The immediate antibiotics prescription rate for the remaining 90 % was not recorded, precluding an estimation of the real incidence of delayed prescribing.

In a New Zealand telephone survey published in 2000, the majority of the participating GPs estimated that less than 10% of their antibiotics prescriptions for RTIs would be delayed prescriptions (36). Five years later, 39% of the GPs reported to have increased their use of delayed prescribing (37, 62), owing partly to awareness of research on the topic (62). Twelve percent of the GPs reported to have decreased their use of delayed prescribing. However, these studies did not measure the actual use of delayed prescribing.

A German direct observation study of primary care consultations for RTIs, published in 2005, found no use of delayed prescribing in the included 273 cases (63).

An observational study by Francis and co-workers on the management of acute cough among adults in primary care, covering 14 networks in 13 European countries (64), is so far the largest study on delayed prescribing in routine care across Europe. The study comprised 3368 consultations for lower RTI, of which 6.3% resulted in a delayed prescription and 46.5% in an immediate prescription. 44.4% of those prescribed delayed antibiotics consumed the antibiotic, and an additional 10.7% used an antibiotic other than the one prescribed at the index consultation during the follow-

up period. Two thirds of the patients consuming their delayed antibiotics started the course without any delay. 71.5% of the patients receiving a prescription for antibiotics to be taken immediately, consumed antibiotics in the study period. There were wide variations between the networks in the use of delayed prescribing, from 0.2% of the consultations in Barcelona to 33.1% in Southampton, with four networks using delayed prescribing in more than five percent of the consultations. Likewise, when prescribing antibiotics, the advice to delay was given in 11.8% of the cases, ranging from 3.5% (Barcelona) to 53% (Southampton). Also, both antibiotic prescribing rates and patients' antibiotic consumption rates varied greatly between the networks.

The study shows that delayed antibiotics prescribing for adults with cough is used infrequently across Europe. It also states that for delayed antibiotics, the consumption rate in routine care is higher than what is found in trials. In addition, the study reveals that patients are not adherent neither when told to delay nor when told to start on antibiotics immediately. The non-adherence to immediate prescriptions constitutes 13 times as many unused antibiotics courses compared to the antibiotics unused due to delayed prescribing.

The included networks were small, and the GPs and patients may have been influenced by local circumstances (64). Also, the study dealt solely with adults with cough. Acute bronchitis is listed as number 7 and cough as number 9 by New Zealand GPs when asked for which symptoms and signs they would give a delayed prescription (62), and a small Canadian study shows that delayed prescriptions are given more frequently to patients with the diagnoses URTI and sinusitis than bronchitis (56). Hence, a lot of areas concerning the effectiveness of delayed prescribing in routine care were not explored in the study.

A concern regarding delayed prescribing in routine care is that the implementation of the strategy would lead GPs to prescribe antibiotics more readily (50), possibly implying that implementation of delayed prescribing would lead to more, rather than less, antibiotics consumption. If the previously mentioned reduction in dispensed antibiotics for children seen in Britain following dissemination of research on delayed prescribing (57) is caused by GPs' increased use of the strategy, this concern is unjustified. However, there may be other explanations for this reduction. In

the same time period, the consultation rate for RTIs among children decreased substantially (65), possibly because of increased parental scepticism towards antibiotics. The same cause may have led to an increased medication non-adherence, giving rise to the observed decrease in antibiotic dispensing rate. Based on the current knowledge, we do not know the effect on antibiotics consumption of implementing delayed prescribing in routine primary care.

Experiences and opinions

When this PhD-project was planned (2006), two qualitative studies on GPs' views on and experiences with delayed prescribing for RTIs had been published. Arroll and co-workers (66) found that a selection of New Zealand general practitioners regarded the strategy useful in decreasing unnecessary antibiotic use, empowering patients and strengthening physician–patient relationships, and that it might be convenient for patients. The GPs were selective concerning which patients they offered delayed prescriptions, but no common criteria were detected. Kumar and co-workers (60) explored why general practitioners prescribe antibiotics for sore throat, and found that delayed prescribing generally was regarded positively, although few described using it.

Recently, a new study on prescribers' views on delayed prescribing (61) revealed that a selection of UK GPs and nurse practitioners preferred reconsultation rather than delayed prescribing. They used the strategy unfrequently, foremostly to manage diagnostic uncertainty but also to avoid conflict. The prescribers felt uncomfortable leaving clinical responsibility to patients, and the authors concluded that alternative ways of communicating empathy, addressing patient beliefs and encouraging self-management should be encouraged.

Among leading researchers on delayed prescribing, there can be found two somewhat diverging views on the rationale behind the strategy – in addition to reducing antibiotics consumption – addressing the two main reasons for inappropriate antibiotics prescribing; (perceived) patient expectation and prognostic uncertainty.

New Zealand professor and general practitioner Bruce Arroll and co-workers at The University of Auckland argue that "Their [delayed prescriptions'] use should be restricted to those patients who request antibiotics or whom their doctor thinks they

want an antibiotic yet does not think one is immediately indicated." (35), hence emphasising the ethical principle of *autonomy*. This is reflected by Arroll et al's trial on delayed prescribing for the common cold (67), a condition for which antibiotics in principle are not medically indicated. Patients were included in the trial if "the [Family Practitioner] thought the patient wanted antibiotics or the patient stated that desire". The authors conclude that delayed prescribing "has the potential to provide gentle education that antibiotics are an unnecessary treatment.". The final aim of the strategy is to teach the patients not to demand antibiotics inappropriately, making delayed prescribing redundant.

Another view emphasises the prognostic uncertainty in RTIs. Professor Paul Little at The University of Southampton, UK, argues that some patients will end up with long lasting or complicated infections if not treated with antibiotics, but for now, there are no precise criteria that can predict who these patients are. In these cases, delayed prescribing serves as a "safety net" or a "backup plan" (68, 69), hence emphasising the principle of *beneficence*. Accordingly, Little and co-workers have conducted trials on delayed prescribing for conditions that may have a bacterial etiology, for which antibiotics may be medically indicated, eg. sore throat (49) and acute otitis media (53).

Opposing these proponents' views, the authors of the Cochrane review on delayed prescribing point out that delayed prescribing has no clinical advantages over no prescribing, and that the latter leads to lower antibiotics consumption. They encourage research on how both patients and doctors better can cope with a "no antibiotics" regimen (43).

Delayed prescribing in guidelines

As a response to the increasing antimicrobial resistance and overprescribing of antibiotics, many countries have developed national guidelines on antibiotic prescribing for RTIs in primary health care. Due to the promising findings in controlled trials, the different guidelines have, to a varying degree, included recommendation of delayed prescribing. The UK's National Institute for Health and Clinical Care (NICE) guideline "Respiratory tract infections – antibiotic prescribing"

(26) of 2008 is the guideline that goes farthest in recommending delayed prescribing. Here, delayed antibiotic prescribing and no antibiotic prescribing are equivalent alternatives for patients with all kinds of "self-limiting respiratory tract infections", unless the patient is at risk of developing complications.

Among the Nordic countries, Norwegian guidelines for antibiotics use in primary health care (70), published in 2008, recommend delayed prescribing for all mild RTIs that might have a bacterial etiology, under certain circumstances. In Sweden, the guidelines on treatment of acute otitis media (71) from 2010 suggests delayed prescribing if a revisit is difficult. Also, the guidelines on treatment of lower respiratory tract infections (72) from 2008 suggests that the GP could consider delayed prescribing if it is difficult to distinguish between bronchitis and pneumonia. Neither Danish (73) nor Finnish (74) guidelines on the treatment of RTIs mention delayed prescribing.

Changing GPs' prescribing

As GPs have the key role in regulating the amount of consumed antibiotics for RTIs in primary care, numerous interventions have been carried out to decrease GPs prescribing of antibiotics. Existing evidence prior to the onset of this study indicated that large effects of interventions to improve clinical practice were rare. (75, 76). Passive dissemination of clinical practice guidelines showed only marginal or no effects on practice (77). More active interventions such as educational outreach visits (78), audit and feedback (79), and multi-faceted interventions (75) were found to be more effective. Computer-based reminder systems also showed promising effects (75).

Newer reviews limited to antibiotic prescribing in an outpatient setting confirmed much of these results; interactive educational meetings were more effective than lectures, and multi-faceted interventions were the most successful in reducing antibiotic prescribing (80). However, educational outreach as well as reminder systems alone produced mixed results (80). Strategies that targeted the management of a single age group or infectious disease were less effective than strategies with broader inclusion criteria (81).

A recent review restricted to physician-targeted interventions to improve

antibiotic use for respiratory tract infections (82) concluded that such interventions generally are effective, with an overall reduction in antibiotic prescribing of 11.6%. Again, it was found that multiple interventions were more frequently effective than interventions using only one element.

We are not aware of reported intervention studies aimed at increasing GPs' use of delayed prescribing. Studies evaluating interventions to improve GPs' antibiotic prescribing habits generally measure the amount of prescribed and not dispensed antibiotics, thereby ignoring any use of delayed prescribing. A large educational intervention study in the UK (83) aimed to reduce antibiotic dispensing in primary care. The authors argue that compared to prescribed antibiotics, dispensed antibiotics is a better proxy for consumed antibiotics, due to the increasing use of delayed prescribing in the UK. However, the intervention did not include any promotion of delayed prescribing.

Aims of the study

The overall aim of this thesis is to explore delayed antibiotic prescribing and its potential in reducing antibiotic use for RTIs in routine primary care. The thesis comprises three studies, each with specific aims:

1. To measure the effects of a GP educational intervention and a computer delayed-prescribing pop-up reminder on antibiotic-dispensing rates. Secondary aim: to identify factors influencing GPs' decisions to issue delayed prescriptions for RTIs and patients' decisions to fill their prescriptions. (The intervention study)
2. To explore GPs' views on and experiences with delayed prescribing in patients with RTIs. (The focus group study)
3. To explore GPs use and patients filling of delayed prescriptions for RTIs, and to investigate the feasibility of the strategy from GPs' and patients' perspective. (The questionnaire study)

Material and methods

This thesis comprises three studies: The intervention study, the focus group study and the questionnaire study. The intervention study is an integrated part of the Prescription Peer Academic Detailing (Rx-PAD) study; it shares the design, participants, randomisation, data handling, sample size, ethics, data security and key elements of the intervention with the Rx-PAD study. Also, the participants in the focus group study and most of the participants in the questionnaire study took part in the Rx-PAD study. Therefore, this chapter starts with a presentation of the Rx-PAD study.

Context: The Rx-PAD study

Design

Cluster-randomised controlled trial. The clusters were existing peer Continuous Medical Education (CME) groups. The groups were randomised to receive either a tailored intervention to support a more rational antibiotic prescribing for respiratory tract infections (84), or to a tailored intervention to reduce inappropriate prescriptions for elderly patients (85). The groups served as control for each other. Throughout this thesis, when describing the Rx-PAD study, I refer to the half of the study using the RTI-arm as intervention group and the prescriptions for elderly-arm as control group. (ClinicalTrials.gov: NCT00272155)

Outcome measures

Primary outcome measures were changes in antibiotics prescription rates and in broad- vs narrow-spectrum antibiotics rates in patients with RTI after the tailored educational intervention.

Participants and randomisation

In Norway, specialists in general practice must apply for renewal of their specialist status every five years. In this renewal process, participation in a CME group is

compulsory. All peer groups (n= 250) on average consisting of seven to eight colleagues located in 11 counties in the southern part of Norway, were invited to participate in the trial. Full participation in the project was rewarded with meriting points for a so called "clinical topic course" necessary for the renewal of the specialty status. GPs using one of four major electronic medical record (EMR) systems (Infodoc®, WinMed®, ProfDoc Vision® or System X®) were eligible for the trial. Of the 98% of Norwegian GP's offices that use EMR systems, 95% use one of these four systems (86).

Of the 250 invited groups, 81 accepted. 37 groups did not respond to the invitation, while the remaining 132 groups did not want to participate. The participating 81 groups were randomised to either the intervention or control group through a manual randomisation strategy based on drawing lots, performed by a person not involved in the study. 40 CME groups were randomised to the intervention group. Before the start of the intervention, one of these CME groups was closed down, resulting in 39 CME groups with 207 GPs in the intervention arm, and 41 CME groups with 243 GPs in the control arm. 382 GPs (intervention/control) delivered data for both baseline and intervention periods.

Intervention

We developed an intervention through a process of identifying inappropriate prescriptions of antibiotics for RTIs. Identification of irrational antibiotic treatment was based on a guideline on antibiotic prescriptions issued by The Norwegian Board of Health 2000 (87). This guideline was distributed to all Norwegian GPs in 2000 and was also available on the Internet. Examples of suboptimal antibiotic prescribing according to this guideline are listed in Table 1.

We recruited 13 GPs to tutor the intervention, each responsible for three CME-groups. The tutors, named Prescription Peer Academic Detailer (Rx-PAD) were recruited on basis of affiliation to the Department of General Practice, University of Oslo, and/or a known interest in RTIs in primary care. The Rx-PADs received a four days pre-study training program, focusing on the evidence of antibiotic treatment of RTI, pedagogical techniques, and how to install and use the software program for data

extraction.

The tailored intervention towards the GPs in the CME groups included two educational outreach visits, each lasting two to three hours, performed by the groups responsible Rx-PAD. In addition, there was a one-day regional seminar gathering 10-15 CME groups.

Table 1: Examples of inappropriate antibiotic prescription patterns according to guidelines by The Norwegian Board of Health 2000

- Uncomplicated acute otitis media (AOM) in children > 1 year of age with symptoms < 3 days
- Acute sinusitis with moderate symptoms < 7 days
- Acute tonsillitis without positive indication of infection caused by group A Streptococcus
- Acute bronchitis (except verified infections caused by Mycoplasma pneumonia or Chlamydia pneumonia)
- Use of broad spectrum antibiotics where penicillin V could be prescribed

In the first outreach visit, the main elements of the intervention were presented, with special emphasis on evidence-based prescribing of antibiotics for RTIs in primary care, choice of first-line drugs, and treatment goals. The participants were encouraged to discuss the advices given. During the visit, a software package was delivered each participant, to be installed on their practice computer. The software extracted data from the preceding 12-month period (01.12.2004 – 30.11.2005) and saved them on a floppy disk, which was to be sent to the study administration. These data were used to generate feedback reports, and comprise the baseline data of this study.

Prior to the second outreach visit, the participants received a personal feedback report, comprising the GPs number of consultations for the various RTI diagnoses, antibiotics prescribing rates, broad-spectrum antibiotics precribing rates, and average numbers/rates for both the CME group and the whole Rx-PAD study.

The second outreach visit took place about two months after the first visit, and

focused on the newly revealed prescription patterns. The Rx-PAD facilitated the discussion within the peer groups, based on individual feedback reports, enabling participants to compare their prescription patterns with the other participants and the overall averages. The discussion aimed at critical reflection towards their own prescription strategies for RTIs and the disclosure of areas where individual improvements were desirable and possible.

Around two months after the second outreach visit, all participants were gathered in regional work-shops where evidence-based rationale behind pharmacological treatment of RTIs in primary care were outlined in more depth on the basis of baseline prescription data. Fifteen months after the first data extraction period ended, a second data extraction of the GPs' prescribings for the preceding 12-months period (01.03.2006 – 28.02.2007) were undertaken. These data comprise the intervention data of this study.

Data handling

Data extraction software was developed for this study. The dataset from each individual GP provided information on number of patient encounters, diagnosis linked to each encounter for patients with a RTI diagnosis, and antibiotics prescription details linked to each encounter for patients with a RTI diagnosis. Diagnosis was based on the International Classification of Primary Care (ICPC-2), and prescription details were based on the Anatomical Therapeutic Chemical (ATC) Classification System with Defined Daily Doses (DDDs).

Because the data did not permit to separate initial encounters from follow-ups, all encounters with an identical ICPC-2 code for an individual patient within a four week period was treated as one RTI episode.

During data analysis, we chose to group ICPC-2 codes reflecting similar illnesses together: upper RTIs (URTIs) and respiratory symptoms (R01–05, 07–29, 74 and 80); ear infections (H01, 71, 72 and 74); and other RTIs (R71, 77, 82 and 83). Other included RTI diagnoses were acute tonsillitis (R72 and 76), sinusitis (R75), acute bronchitis (R78) and pneumonia (R81).

Sample size

Based on previous studies, we anticipated an antibiotics prescribing rate for RTIs of 27% (88) and an intra-cluster correlation coefficient of 0,085 (89). We expected an average of seven GPs per CME group, and 300 encounters for RTIs per GP during the intervention period. A reduction in antibiotics prescribing rate for RTIs of one third was considered clinically relevant. Given these figures and applying an 80% power and a 5% significance level, we found an intervention sample size requirement of 31 CME groups and a corresponding number of control groups.

Ethics and data security

The participating GPs gave their written informed consent. In order to use patient identification data, The Directorate for Health and Social Affairs approved dispensation from the health-professional secrecy. Approval from The Norwegian Social Science Data Services (NSD) was obtained, which implied acceptance to extract prescription data. The Regional Committee for Research Ethics in Oslo, Norway, approved the study (S-05272).

Paper I – The intervention study

Design

Cluster-randomised controlled trial with an embedded controlled trial.

Main outcome measure

Dispensed antibiotic prescriptions as a proportion of prescribed antibiotic prescriptions.

Interventions and randomisation

The cluster-randomised controlled trial – educational intervention

A recommendation of delayed antibiotic prescribing was included in the educational intervention of the Rx-PAD study. At the first outreach visit, the Rx-PADs presented results from RCTs on delayed prescribing, and encouraged a discussion on the topic. At the regional work-shops, I held a 30-minute lecture on delayed prescribing, and presented the strategy as a possible tool to decrease the patients use of antibiotics.

The embedded controlled trial – pop-up-reminder intervention

In the educational intervention group, a subordinate trial was embedded. For two of the four eligible EMR systems (WinMed® and ProfDoc Vision®), the software package included a pop-up window to appear on the computer screen when antibiotics were prescribed, expect from antibiotics merely used for conditions other than RTIs (nitrofurantoin, pivmecillinam, trimetoprim). The window contained a question on whether the prescription was a regular or a delayed prescription (Appendix E).

The Rx-PAD study protocol (84) describes the pop-up software merely as a tool to identify delayed prescriptions. However, during the further planning of the study and before the intervention took place, it became evident to us that the pop-up might have an effect on the delayed prescribing rate and thereby on the dispensing rate.

GPs with the two other EMR systems (Infodoc® and System X®) served as control for the pop-up intervention group. As such, there was no randomisation in

this trial. This was chosen out of convenience, as the development of software for each EMR system was resource-intensive. Among Norwegian GP's offices using one of the four EMR systems, approximately 76% use WinMed® or ProfDoc Vision®, while 24% use Infodoc® or System X® (86). In the Rx-PAD intervention group, 69% of the GPs (107/156) had the pop-up-reminder software installed, while 31% (49/156) did not have the reminder.

There were no statistically significant differences between the pop-up intervention group and its control regarding GP's gender, age, speciality status, practice location, practice type, antibiotic prescription rate at baseline or number of patient encounters. At baseline, the intervention group GPs had more female patients (59,6% vs 56,8%), more patients with uppert RTI/RTI symptoms (25,7% vs 23,3%), pneumonia (11% vs 9,7%) and other RTIs (5,6% vs 3,5%) and fewer patients with tonsilitis (14,1% vs 16%) and lower RTIs (15,3% vs 17,8%) than the control GPs. There were no significant differences between the two groups regarding the consulting patients' age.

Data handling

The prescription data used in this study equals the EMR system data described in the Rx-PAD study section. In addition, for the pop-up-reminder intervention group, the software package extracted data on whether a prescription was to be filled immediately, or whether it was a delayed prescription, and for how long the patient should wait before deciding to use the antibiotics.

In order to register whether a prescription was picked up at a pharmacy, data from the EMR systems were merged with data provided by the Norwegian Prescription Database (NorPD). NorPD is a national registry including data for all prescription drugs issued at Norwegian pharmacies, established in 2004 (90). The merging was based upon the prescribed antibiotics' ATC code, the patient's Birth Number (the unique identification numbers for Norwegian citizens), the GP's unique Health Personnel Register Number, and dispense date within 21 days after prescription date.

As the main outcome measure in this study was prescription pick-up rate and

not prescribing rate, our level of observation was *patient encounters resulting in an antibiotics prescription*, as opposed to *RTI episode with or without antibiotics prescribing* used in the rest of the Rx-PAD study.

Participants

382 GPs delivered floppy disks with extracted prescription data from both the baseline and intervention periods (88790 prescriptions). Of these, 33 GPs were excluded because they did not get data in return from NorPD due to late delivery of floppy disks to the project administration (29 GPs), or because none of the patients' Birth Numbers were registered in their EMR system (4 GPs). 14 GPs in the educational intervention control group were excluded because they – by a mistake – were equipped with the pop up reminder-software (12 GPs) or because they got NorPD data only for patients > 70 years (2 GPs).

1633 prescriptions were excluded because the corresponding patients were not registered with a Birth Number in the GPs EMR system, hence, these prescriptions could not be merged with NorPD data. Also, 3045 prescriptions were excluded because the ATC number was not properly registered in the GPs EMR system, which impeded both the pop-up software function and the merging with the NorPD data.

After the establishment of the NorPD register 01.01.2004, the Norwegian GPs were required to fill in their Health Personnel Number and the patients' complete Birth Number on the prescription. At the start year of the RxPAD study, 3.7% of all dispensed medications registered in the NorPD lacked Birth Number, while the corresponding proportion at the end of the study was 1.9% (Personal communication, NorPD 20110812). This would account for an artefact increase in pick up rate from baseline period to intervention period for some of the GPs.

Most of the prescriptions lacking Birth Number in this study were excluded on basis of lacking number in the GPs EMR system. However, included prescriptions may have been printed out without Birth Number.

Five GPs in our material had an increase in pick up rate > 30 percentage points from baseline to intervention period, while the GP with the largest decline had a 17 percentage points decrease. We assume that this is an artefact due to the decrease in

missing Birth Numbers from baseline to intervention period registered at the NorPD. In order to compensate for this error, we chose to exclude the five outlying GPs with the highest pick-up rate increase.

The figure in Appendix A displays the participating GPs in relation to the GPs participating in the other two studies.

Statistics

Two logistic regression analysis were performed with the dependent variable being whether the prescription was picked up at a pharmacy or not, and whether the GP issued the prescription as a wait-and-see-prescription or not.

We included random intercepts at two levels: GP and CME group. A model including random slopes at the GP level (i.e. allowing patient variables age, gender and diagnoses to vary amongst GPs) did not fit the data due to numerical overflow. The included random effects were statistically significant.

Adjusted odds ratios can not approximate the risk ratios when the incidence of the outcome of interest is common (>10%) (91). As our outcome – prescriptions being dispensed – is very common, we approximated the risk ratios from the odds ratios using a standard correction method (91).

A significance level of 5% was applied. The descriptive analyses were performed using PASW Statistics 18 (www.spss.com), while the multilevel regression analyses were performed using STATA 11.2 (www.stata.com).

Paper II – The focus group study

Participants

The data in this study were generated in five focus group interviews with GPs participating in the antibiotic arm of the Rx-PAD Study. One of the groups was a purpose-constructed group assembled at a general practitioner congress, while the other four groups were existing CME groups.

The CME groups and the individual GPs in the purpose-constructed group were recruited using a purposeful sampling strategy, aiming for variety in the sample with respect to geography, age, gender, and antibiotic prescribing rates. Also, we sought for homogenity in the groups with respect to gender (92). One of the groups consisted of only women, one group of only men, while the other three groups were mixed.

The CME group secretaries and the participants in the purpose-constructed group were approached first by e-mail, then by telephone as a follow-up of the e-mail. The sample size of five focus groups was a result of the strategic sampling of a minimum of one pilot group (which also was a male only group), one female CME group, two mixed CME groups from different geographical areas, and one non-CME group. When these groups interviews were conducted, we experienced saturation in the data, as the latest interviews yielded little new information. As a result, we stopped the recruitment.

The focus groups consisted of from three to eight members, with a total of 33 participants. There were 15 female GPs, and the mean age was 50 years. Table 1 in paper II presents the characteristics of the participants.

The participants were granted anonymity. As no patients were involved in this study, we did not apply for ethical approval by The Regional Committee for Research Ethics.

The figure in Appendix A displays the participating GPs in relation to the GPs participating in the other two studies.

Interviewer's role, background and perspectives

I brought some important preconceptions and beliefs with me into this study. On

basis of several RCTs on delayed prescribing showing the strategy's ability to decrease antibiotics consumption, delayed prescribing was set to be an integrated part of the educational intervention in the Rx-PAD study. Being a part of the Rx-PAD research team, I shared the view that there is an overprescribing and overuse of antibiotics for RTIs in Norway, and that advocating delayed prescribing among GPs might decrease this overuse. Being aware of the relatively low antibiotics prescribing in Norway (9), I expected that Norwegian GPs were concerned with prudent antibiotics prescribing and would welcome a strategy that could decrease the use even further, but also that the GPs might be content with the relatively low antibiotics use. I assumed that the participants would have divergent views on strategy, and that proponents of prudent prescribing and patient-centeredness would be most positive.

I presented myself in the focus groups as a general practitioner and PhD-student working with a project on delayed prescribing within the Rx-PAD study. Most of the participants had already met me at the Rx-PAD study regional work-shop, and heard me recommend delayed prescribing as a potentially effective strategy to lower unnecessary antibiotics use. Consequently, the participants might have expected that I wanted to hear positive statements on the strategy. Hence, I underlined that I was especially interested in negative experiences, side effects and limitations of delayed prescribing.

Interviews

We developed an interview guide with open-ended and wide-ranging questions, covering experiences and views of the GPs on delayed prescribing (Appendix B). The group interviews were conducted between October 2006 and September 2007. We considered focus group interviews as an appropriate method to highlight views and divergent opinions (93). I acted as moderator for four focus group interviews while the co-supervisor was moderator for one interview. The co-supervisor was also present as an observer at two of the interviews I moderated.

The first group served as a pilot, and the interview guide was slightly moderated after the pilot interview. Each of the focus group interviews lasted for 45–75 minutes, and took place where the CME groups usually held their meetings. GPs were

encouraged to share their views in an open discussion, and the moderator ensured that all participants were heard. The discussions were audio-recorded digitally. Preliminary findings from the first interviews were fed back into later focus groups for further discussion. The pilot interview was analyzed together with the other four interviews.

Analysis

Audio-recordings were transcribed verbatim. The material was analysed using a procedure for content analysis referred to as "systematic text condensations", inspired by Giorgi (94) and modified by Malterud (95). The procedure comprise the following four steps: (i) reading all the material to obtain an overall impression, actively bracketing previous ideas and preconceptions, and identifying main themes in the material; (ii) identifying units of meaning, representing different aspects of GPs' experiences with delayed prescribing within each main theme, and coding for these; (iii) condensing and summarising the contents of each of the coded groups; and (iv) generalising descriptions and concepts about specific themes. All the authors took part in the analysis, and met to discuss the meaning of the data and the interpretation of the material. NVivo7 software (www.qsrinternational.com/products_nvivo.aspx) was used for coding. Quotes from interviews were translated from Norwegian into English by the authors.

Some of the items from the interview guide were brought in as main themes in step (i), while the other main themes emerged from the material. In the analysis, we sought to focus at the GPs hands-on experience and views on the delayed prescribing strategy in a clinical setting. Thereby, we left out a small number of main themes after step (ii), notably themes concerning the pop-up-reminder software and the concept of power in the doctor-patient relationship.

Paper III – The questionnaire study

Subjects and setting

We translated and adopted a questionnaire on patients' response to delayed prescription used in a previous study (32) (Appendix D), and developed a corresponding GPs' questionnaire comprising questions on background information (patients age, gender), diagnosis, reason for issuing wait-and-see prescription, reasonableness of the strategy, and the GPs assumption on patient satisfaction, patient demand for antibiotics and whether the patient was going to use the prescription (Appendix C). The GP questionnaire was piloted.

As part of the one-day seminar described in the Rx-PAD study section, I gave a 30 minute lecture on the evidence regarding delayed prescribing, and invited the GPs to participate in, and recruit patients to, a questionnaire survey. Of the approximately 150 GPs who attended the seminar, 58 GPs agreed to participate. In addition, 16 GPs affiliated to the Department of General Practice, University of Oslo, were given the same lecture, and agreed to participate (Figure 1).

Eligible patients were those of any age who consulted the GP for a RTI, and to whom the GP found it appropriate to offer a wait-and-see prescription. In the course of the consultation, the GP handed the patient an antibiotic prescription together with a patient questionnaire, an information leaflet with a consent form, and a prestamped envelope. The patient was instructed to wait for a certain amount of time, chosen by the GP, before deciding whether to take the antibiotics or not. Apart from this, we did not standardise the way of practicing the delayed prescribing strategy, as to what advice the GP was to give the patient, selection criteria etc. The information leaflet ensured that the patients received a minimum of identical information.

The patient questionnaire was to be filled once the patient had made the decision whether to use the antibiotics or not. After the consultation, the doctor filled the GP questionnaire. Patients were rewarded with a scratch card upon responding, while the GP would receive a gift card for a CD when they had recruited 10 patients. Recruitment took place during April 2006 through June 2008. The Regional Committee for Research Ethics in Oslo, Norway, approved the study (S-05272).

The figure in Appendix A displays the participating GPs in relation to the GPs

participating in the other two studies.

Statistical analysis

Chi square test was used to compare those patients who reported to consume antibiotics and those who did not, with regard to both patient factors (demographic characteristics, presenting symptoms, expectations, confidence in deciding whether to use the prescription) and GP factors (diagnose, reason for giving wait-and-see prescription, reasonableness, and impression of expectations and use of the prescription). Logistic regression analysis was performed with the dependent variable being whether the patient reported to consume the antibiotics or not. Further, we compared cases where the GP found delayed prescribing very reasonable and cases where where the GP did not. A significance level of 5% was applied. Analyses were performed using SPSS 14 and 18.

Material

Out of a total of 68 GPs, 49 (72%) recruited on average 8.5 patients each (median 6; span 1-34). 19 (28%) GPs recruited no patients. We received 413 responses from GPs and 332 responses from patients. Five patients informed that they did not want to participate, and consequently we removed the corresponding GPs responses. For five of the patient responses, we did not receive a corresponding GPs response, resulting in 327 response pairs and a patient response rate of 80%. 17 response pairs were excluded because the GPs had included patients who were treated for other conditions than RTIs, and an additional six response pairs were excluded because the patients failed to answer whether they had taken antibiotics. 304 response pairs remained for analysis. We grouped diagnoses according to previous studies on RTIs (18, 25), described in the Rx-PAD methodology section of this thesis, with the exception that R80 Influenza was categorised as "Other respiratory diagnoses" and that R78 Acute bronchitis and R81 Pneumonia was grouped together in one category; "Lower RTIs".

Summary of results

Paper I – The intervention study

Høye S, Gjelstad S, Lindbæk M.

Effects of interventions to promote delayed prescribing for respiratory tract infections on antibiotic-dispensing rates.

Provisionally accepted, Br J Gen Pract.

The aim of this paper was to measure the effects of a GP educational intervention and a computer delayed-prescribing pop-up reminder on antibiotic-dispensing rates. Secondary aim: to identify factors influencing GPs' decisions to issue delayed prescriptions for RTIs and patients' decisions to fill their prescriptions.

At baseline, 92% of antibiotic prescriptions were filled at pharmacies. An educational intervention on prudent antibiotic prescribing including a recommendation of delayed prescribing, combined with a pop-up reminder on delayed prescribing, resulted in a 3% reduction in approximated risk (RR 0.97, 95% CI 0.95 to 0.99) of prescribed antibiotics being dispensed, without any increase in antibiotic prescribing rate. The educational intervention alone produced a 1% reduction in approximated risk (RR 0.99, 95% CI 0.97 to 1.01) of antibiotics being dispensed. Delayed prescriptions were filled in 59% of all cases.

Having pneumonia or acute tonsillitis and being of older age increased the odds of the prescription being filled at a pharmacy. Patients with acute sinusitis, otitis media, or upper RTI and symptoms and patients of younger age had the highest odds of receiving a delayed prescription.

We conclude that promoting delayed prescribing through lectures and group visits alone is insufficient to influence medication-dispensing rates. However, a constant reminder of the delayed-prescribing option through a computerised pop-up reminder results in a small, though statistically significant decrease in the number of filled prescriptions. This strategy for decreasing antibiotic consumption is most effective in children and in adults with otitis, sinusitis, or upper RTIs.

Paper II – The focus group study

Høye S, Frich JC, Lindbæk M.

Delayed prescribing for upper respiratory tract infections: a qualitative study of GPs' views and experiences.

Br J Gen Pract. 2010; 60: 907-12.

The aim of this paper was to explore GPs' views on and experiences with delayed prescribing in patients with acute upper respiratory tract infections.

We found that GPs viewed delayed prescribing as a method that was well suited to the spirit of clinical work in general practice, although their views differed on the usefulness of the strategy. GPs who endorsed delayed prescribing emphasised shared decision making and the opportunity to educate the patient. GPs who were negative said that they mainly used the strategy in what they experienced as an uncomfortable situation of being forced to prescribe.

Mild and mainly harmless conditions that might be of bacterial origin, such as acute sinusitis and acute otitis, were considered most suitable for delayed prescribing, as opposed to conditions that were considered as purely viral, such as common cold. An important argument for issuing a wait-and-see prescription was to help the patient to avoid seeking after-hours care, especially during holidays and weekends.

For issuing a wait-and-see prescription, the GPs required that the patient was 'knowledgeable', able to understand the indications for antibiotics, and motivated for shared decision making. GPs emphasised the importance of informing the patient thoroughly when issuing a wait-and-see prescription.

We conclude that delayed prescribing is not endorsed by all GPs, but the strategy appears to be a feasible approach among informed patients with early symptoms of mild URTIs of a possible bacterial origin, such as acute otitis and acute sinusitis. Informing the patients properly while issuing wait-and-see prescriptions is essential.

Paper III – The questionnaire study

Høye S, Frich JC, Lindbæk M.

Use and feasibility of delayed prescribing for respiratory tract infections: A questionnaire survey.

BMC Fam Pract 2011; 12: 34.

The aim of this paper was to explore GPs use and patients uptake of wait-and-see prescriptions for RTIs, and to investigate the feasibility of the strategy from GPs' and patients' perspectives.

General practitioners who have been informed about the use of wait-and-see prescriptions in RTIs, most often use the strategy in cases of acute sinusitis and acute otitis media. These are also the diagnoses for which the GPs find the strategy most reasonable. The reported reason for issuing a wait-and-see prescription is most commonly uncertainty about indication for antibiotics. Patients receiving a wait-and-see prescription are confident in the decision whether to start taking the medication, and half of the patients report to consume the antibiotics. Feeling very ill, having fever, and being more than 16 years of age predict consumption of antibiotics, while reporting nasal congestion is negatively associated with consuming antibiotics.

We conclude that most patients and GPs are satisfied with the delayed prescribing strategy. The patients' age, symptoms and malaise are more important than the diagnosis in predicting antibiotic consumption. The GP's view of the method as a reasonable approach depends on the patient's diagnosis. In our setting, delayed prescribing seems to be a feasible strategy, especially in cases of sinusitis and otitis. Educational efforts to promote delayed prescribing in similar settings should focus on these diagnoses.

Discussion

Methodological considerations

Overall methodological discussion

This thesis is concerned with the GPs; their attitudes, experiences, and prescribing behaviour. We did not set out to measure the clinical effect of delayed prescribing, as this is well documented in RCTs. Patients have contributed with symptom description and reported antibiotics consumption in the questionnaire survey, and with actual prescription filling data in the intervention study. However, the patient level mainly serves as a tool to measure how the GPs' behaviour affects antibiotics dispensing.

Sampling / External validity

The participants in all the three studies – except for a small number of GPs taking part in the questionnaire study – were members of CME groups who through their group coordinator had agreed to participate in a quality improvement study; the RxPAD study. We do not know if the groups practiced a democratic decision on whether to participate, in which a minority of the members might have objected but still were obliged to participate, or whether the decision to participate had to be unanimous among the group members. Still, one may argue that the 328 participants, constituting 80 CME groups, might hold more positive views towards quality improvement projects and be more ready to change prescribing patterns compared to the 169 groups who rejected or did not answer the invitation. This may challenge the generalisability of our results. Therefore, we did calculations to compare the participants with the non-participants. As readiness to change or attitudes towards delayed prescribing was not measured among non-participants, our best measurement was antibiotics prescription details. This is by no means a perfect measurement, but there is reason to believe that GPs interested in antibiotics stewardship also prescribe less antibiotics and a higher rate of narrow-spectrum antibiotics. We have no data on numbers of RTI encounters by non-Rx PAD GPs, thereby we can not calculate prescribing rates. However, the NorPD database offers total numbers of antibiotics prescriptions and the narrow-spectrum/broad-spectrum antibiotics rates for all

Norwegian specialists in general practice, and these data show no significant differences between RxPAD participants and no-participants (20).

One may also argue that the participants in the focus group and questionnaire studies were additionally positive towards methods that aim to lower the use of antibiotics in general, and delayed prescribing in particular, as they had agreed to take part in studies on delayed prescribing. However, in the focus group study, both GPs with high and low antibiotic prescribing rates were included, and both positive and negative views towards the strategy were exposed. In the questionnaire study, we did not record the participants antibiotic prescribing rates. A substantial proportion of the participants (39%) recruited only 1-4 patients, indicating that they seldom used delayed prescribing. The results from the questionnaire study are understandably generalisable only to GPs who are sufficiently positive towards delayed prescribing that they actually use the strategy to a greater or lesser degree.

As participants in the RxPAD study, most of the focus group and questionnaire study participants had attended the one-day seminar where I recommended delayed prescribing as a strategy to lower unnecessary antibiotics use. I tried not to recommend delayed prescribing for certain patient groups, diagnoses or situations. Still, my lecture may have influenced on the GPs views and behaviour.

Triangulation

The term method triangulation, often used in qualitative research, refers to using more than one method when studying a phenomenon (96). Triangulation may reduce the risk of bias and enhance the validity of qualitative research. This thesis builds on method triangulation, as three different methods are used to explore delayed prescribing.

All the focus group participants and most of the questionnaire survey participants also participated in the Rx-PAD study. This might be seen as a weakness, as described in the previous section, but also as a strength, as the coherence between the three studies shows that the GPs actual use of delayed prescribing corresponds to what they tell they do in the focus group and questionnaire studies. As such, the intervention study validates the findings in the focus group and questionnaire studies.

All the three studies in this thesis were carried out simultaneously, for practical and logistic reasons. A better approach would have been to conduct the focus group study prior to the two other studies. In the questionnaire study, when asked why they issued a delayed prescription, the large majority of the GPs chose the option "Uncertainty about indication for antibiotics" (69% of the cases), and the option "Other reasons" was chosen in as many as 14% of the cases. Based on the results from the focus group study, more relevant options such as "Short duration of symptoms" and "Patient convenience" might have yielded more accurate results. Also, in the intervention study, results from the qualitative study could have been presented at the group meetings, facilitating an open discussion on potential reluctance towards delayed prescribing.

Diagnosis grouping

In our studies, we chose to group ICPC-2 codes reflecting similar illnesses together, in the same manner as earlier research done by the same research members. The most questionable factor of this grouping was to put all the symptom diagnoses in the category Upper RTI, as some symptom diagnoses might be closer related to other categories. The obvious examples of this are R05 Cough (might belong to category Lower RTI), R09 Sinus symptom/complaint (might belong to the category Sinusitis), and R21 Throat symptom/complaint (might belong to the category Tonsillitis).

In the questionnaire survey, 17 (28%) of the 60 prescriptions in the Upper RTI category where symptom diagnoses. In the intervention study, of the 17616 prescriptions in the Upper RTI category, 8310 (47%) were symptom diagnoses, of which 4710 were R05 Cough, 494 were R09 Sinus symptom/complaint and 2134 were R21 Throat symptom/complaint. The results in both studies would have been different if we choose other ways of grouping the diagnosis. However, we have to assume that the GPs, when diagnosing the patient, chose symptom diagnoses when the illness did not meet the criteria of a certain disease, and that including e.g. R09 Sinus symptom/complaint in the Sinusitis category would distort the results from this category. An alternative solution would be to include a Symptom diagnoses category, but we wanted to keep the number of categories as low as possible. The result is that

the category Upper RTI and RTI symptoms is a heterogenic group of diagnoses, and this must be taken into account when comparing our results with other research.

The diagnostic problem

Most quality improvement studies and randomised, controlled trials on RTIs in primary care are diagnosis specific, ie they deal with one specific respiratory tract infection, with detailed inclusion and exclusion criteria (22-24, 97). In our studies, patients with all kinds of RTIs were included, and the registered diagnoses were based purely upon the individual GPs assessment, without any explicit diagnostic criteria. There are several problems connected to this approach. The diagnostic assessment and accuracy may vary greatly from GP to GP – what one GP diagnoses as acute sinusitis, another GP may diagnose as sinus symptoms, or use the broader category of upper respiratory tract infection (even though the latter diagnosis, according to ICPC-2, exclude acute sinusitis). The inter-rater reliability of the ICPC-2 is found to be only fair to moderate on the single code level (98).

Also, it is documented that GPs may chose a treatment option prior to choosing diagnosis, and thus be in danger of choosing a diagnosis that "fits" with the treatment given (99, 100). In addition, for using some of the functions in the EMR systems (e.g. printing a sickness certificate), one has to specify a diagnosis. If one needs to use any of these functions early in the consultation, one may choose a "preliminary" diagnosis prior to anamnesis and examination, without correcting the diagnosis if the anamnesis or examination proves it wrong.

Finally, participating in a educational study on appropriate antibiotics prescribing and receiving a personal prescribing patterns report, may have altered the diagnostic process, so that diagnosing may vary from baseline to intervention period. For example, our message that the diagnosis of acute bronchitis does not warrant antibiotics may have caused GPs to rather diagnose a lower RTI as a pneumonia if the GP chooses to treat the condition with antibiotics. This possible shift in diagnosing is an unintended, but probable effect of the intervention, and is yet to be explored.

The use of the diagnosis *R83 Respiratory infection other* demonstrates some of the problems mentioned above. According to the full version of the ICPC-2, the diagnosis

includes "chronic nasopharyngitis; chronic pharyngitis; chronic rhinitis not otherwise specified; diphtheria; empyema; epiglottitis; fungal respiratory infection; lung abscess; protozoal infection (without pneumonia)" (101). These conditions are either very rare in primary care, or they are not primarily bacterial infections. Still, in the intervention study, *R83 Respiratory infection other* constitutes 4182 (5,8%) of the 72512 prescriptions, making up 89% of the 4680 prescriptions in the "Other RTIs" category. In the questionnaire survey, the same diagnosis constitutes two (0,7%) of the 304 wait-and-see-prescriptions, making up 15% of the 13 prescriptions in "Other RTIs" category. The Norwegian main title of *R83* is "Luftveisinfeksjon IKA", directly translated "Respiratory tract infection NOS" (Not Otherwise Specified). The reason for this most probable overuse of the R83 diagnosis in the intervention study may be lack of knowledge on the diagnostic criteria, use of "preliminary diagnosis", diagnostic uncertainty and lack of time. In the questionnaire survey, the GPs were to fill the diagnosis onto the questionnaire sheet, and this may have given better time for an accurate diagnosis.

All in all, we chose to include all RTIs and to let the GPs use their own diagnostic criteria, both to get an overall picture of delayed prescribing for RTIs, to mimic the everyday practice, and because the study would be impossible to implement in such a large scale if the GPs were to adhere to explicit diagnostic criteria.

Paper I – The intervention study

There was a relatively large exclusion rate in this study; from the 382 GPs delivering data on 88790 prescriptions from both baseline and intervention period to the included 328 GPs (14,1% excluded) with 72512 prescriptions (18,3% excluded). This is largely caused by late delivery of data from some of the GPs, erroneous software installation, and lacking information preventing the merging of the EMR and the NorPD dataset. There were significantly more female GPs (34% vs. 22%) and specialist GPs (89% vs. 80%) among the included GPs. On all other GP characteristics, including antibiotic prescription rate, there were no significant differences between included and excluded GPs.

The main outcome variable; dispensing rate, is based on achieved data in relation

to non-achieved data; when NorPD data is lacking on one specific prescription, we assume that that prescription has not been dispensed at any pharmacy. However, lacking data may have other causes; missing or wrong information on the prescription, missing or wrong registration at the pharmacies, and failures in the data flow between the databases. We have actively and intensively sought for such errors, and eliminated the ones we have found. Still, there might be hidden errors resulting in a falsely low dispensing rate. However, the baseline dispensing rate of 92% is in accordance with the levels found in other studies. Also, the different dispensing rates we have observed in the intervention and control groups would be equally influenced by any falsely low dispensing rate.

The pop-up reminder and -registration software did not pop up for every prescription issued by the pop-up intervention GPs; the GPs issued 12.435 prescriptions in the intervention period, while the software registered 10.860 (87%) of these prescriptions as either delayed og regular. This may be due to change of hardware during the intervention period, or that some of the GPs may have uninstalled the software or printed out prescriptions from other computers than their own. We used the intention to treat-principle, hence all prescriptions issued by GPs who got the pop-up software installed, were analysed as belonging to the pop-up intervention group.

When a prescription is not picked up at a pharmacy, this is not necessarily an indication that the corresponding patient has taken an active choice not to use the antibiotics. Ekedahl and Månsson interviewed Swedish patients not claiming their electronically transmitted prescriptions (102). 17 of the examined prescriptions were for antibiotics, and for 9 of these, the reason for not claiming it was exclusively related to the electronic transmission. For the remaining eight prescriptions, half of them were delayed / "as-needed" prescriptions, while the other four remained unclaimed because the patient had another prescription for the same medication/ had leftovers /got a double set of prescriptions (Personal communication, A. Ekedahl). In spite of very low numbers, the findings illustrate that unfilled antibiotics are not equivalent to delayed prescriptions, or to a situation in which the patient is rid of the disease. This must be taken into account when considering our results.

We have used the primary non-adherence, ie the proportion of prescribed antibiotics not dispensed at pharmacies, as our outcome measure. In our analyses, we have not separated between dispensed delayed prescriptions and dispensed regular or uncategorised prescriptions. This raises the question of whether primary non-adherence of antibiotics for RTIs in primary care is a wanted or unwanted phenomenon. In the research literature, undispensed delayed prescriptions are obviously wanted, while non-adherence is said to contribute to worsening of disease and increased health care costs (103), and in the case of RTIs, to waste health resources, to possibly impact on health outcomes, and to result in leftover antibiotics that can be used as self-medication with the risk of increasing the pressure for antibiotic resistance (104), ie an unwanted phenomenon.

As there was no clinical monitoring of the patients in our studies, we have no account of the clinical outcome for patients who did or did not fill their antibiotics prescription. However, as seen in RCTs on delayed prescribing, there are only marginal differences in clincal outcome for patients receiving immediate, delayed or no antibiotics (43). Also, Francis et al found no differences in clinical outcomes between fully adherent and not adherent patients prescribed antibiotics for acute cough (104). As such, an increase in unfilled prescriptions as a result of the intervention should not be of clinical concern.

The pick-up rate is a proxy for what would be the most relevant measure; antibiotics consumption rate. Prescriptions may have been picked up without the patient having taken the medication, and also, patients may have acquired and consumed antibiotics from other sources (105) and hence omitted to fill the prescription registered in the EMR dataset. However, registered antibiotics dispensing rate is the closest we can get to consumption rate without using patient self-report, which may be unreliable (106) and would be too resource-intensive for such a large trial, or electronic measurement devices (106), which also would be impossible to implement in terms of resources.

Paper II – The focus group study

We used established CME groups as focus groups, for several reasons. First, we

expected that the participants knew each other well and respected each others views, creating a atmosphere in which the participants could speak freely. Second, the Rx-PAD Study intervention was conducted on a CME group level, the members had already revealed and discussed each others prescribing patterns, and might challenge discrepancies between expressed beliefs and actual behaviours. Third, the CME groups had an established form, meeting location and meeting time, and the members were given meriting points also for the focus group interview, warranting that the participants would show up and stay for as long as the interview lasted. On the other hand, we anticipated that divergent views also might be suppressed in established groups, which led us to include one purpose-constructed group (93).

Reflexivity

My role and my preconceptions may have had an influence on the participants expressed views on delayed prescribing. In order to challenge our own preconceptions, all authors took part in the analysis, and we agreed on the results. In addition to having some of my expected findings confirmed, I also discovered diverging and unexpected views and experiences.

My preconception that the participating GPs were concerned with prudent prescribing was confirmed. However, I was surprised to find that delayed prescribing was not foremostly seen as a means to lower unnecessary antibiotics use, but as a practical solution at the individual patient level, e.g. helping the patient avoid seeking after-hours care. As expected, there were divergent opinions on the strategy, but we did not find that the proponents were more concerned with prudent prescribing than the opponents. Rather, both sides made references to prudent prescribing to support their view.

Paper III – The questionnaire study

The response rate (80%) was relatively high compared to a similar study by Edwards (32). This may be caused by the difference in deliverance of the questionnaire; in our study, the GP handed the patient the questionnaire, while in Edwards' study, the questionnaire was sent by second class post.

The GP and patient questionnaires were not validated. We acquired a patient questionnaire used in the study by Edwards (32), in order to be able to compare our results.

The aim of this study was not to explore clinical outcomes and safety of the delayed prescribing strategy, and potential differences in treatment outcomes for different diagnoses have not been investigated. This study does not allow to directly compare the use of wait-and-see prescriptions with the use of prescriptions for antibiotics to be taken immediately, since we have no record of the latter.

As in all questionnaire surveys, our results depend on the respondents report, and not necessarily on their action. The patient questionnaire and information leaflet were carefully constructed to avoid an impression that not picking up the prescription would be the preferred solution, as to minimise a social desirability bias (107). Still, the reported antibiotics consumption rate of 46% may be an underreporting of what actually happened.

Acceptability of delayed prescribing

In the focus group study, we found that GPs viewed delayed prescribing an acceptable strategy, but to a varying degree. The GPs who endorsed delayed prescribing the most, found that it was useful in empowering and educating the patient. Other GPs said that they mainly used delayed prescribing in what they experienced as an uncomfortable situation of being forced to prescribe antibiotics, and were more negative towards the strategy.

The questionnaire study strengthens the validity of these results. In the few cases where delayed prescribing was used because of treatment disagreement with the patient, the GP was significantly less satisfied with the strategy compared to cases where delayed prescriptions were issued for other reasons.

The findings are similar to those of Arroll et al (66), who found that delayed prescribing was considered a useful strategy in decreasing unnecessary antibiotic use, empowering patients, strengthening the physician–patient relationships, and securing convenience for the patients. However, Arroll's study setting was patients with common cold, whereas our participants did not see this diagnose as suitable for

delayed prescribing.

In 2011, Peters et al (61) conducted a comprehensive qualitative study of the usefulness of the delayed prescribing strategy within UK primary care. The participants commonly found RTI consultations confrontational, due to a perception that patients expected antibiotics, and the prescribers did not trust patients to fill the delayed prescriptions only if the condition worsened. The prescribers generally felt uncomfortable about using delayed prescribing, and reported using the strategy infrequently.

These results are similar to the views held by the GPs most reluctant to delayed prescribing in our focus group study. When stating that delayed prescribing mainly was acceptable to our selection of GPs, this is based on a setting where the GPs generally did not consider RTI consultations as confrontational.

Accordingly, the acceptability of delayed prescribing varies both between different settings and different GPs. In the intervention study, delayed prescribing were more often used by women, group practitioners and GPs without speciality in general practice than men, solo practitioners and GP-specialists. However, none of these differences were significant in the adjusted logistic regression analysis. A common view among the focus group GPs was that doctors with a paternalistic decision-making style would not accept the strategy. However, the results do not support that GPs reluctant to delayed prescribing have a paternalsitic style, neither that delayed prescribing was used to ensure the opposite decision-making style (44); the informed choice model, or the middle ground between these models; the shared decision-making model. A strong view among the participants was that patients receiving a delayed prescription should be instructed thoroughly in the criteria for starting to take the antibiotics. Hence, delegation of authority, rather than sharing the decision or informing for a free choice, is a relevant term for the GPs understanding of delayed prescribing. Although the participants made references to informing and empowering patients as an argument for delayed prescribing – terms associated with patient-centered care and shared decision-making – the GPs generally held that the decision whether the patient should consume the antibiotics was theirs, through clear instructions and based on the course of the condition. Also, the decision whether to

issue a delayed prescribing was commonly referred to as the GPs decision. When diverging views on the necessity of antibiotics led to delayed prescribing, the GP referred to this as a lost discussion rather than a common agreement.

Charles et al (44) have suggested four key characteristics of shared decision-making: 1) At least two participants (physician and patient) are involved. 2) Both parties share information. 3) Both parties take steps to build a consensus about the preferred treatment. 4) An agreement is reached on the treatment to implement. Elwyn et al (45) have questionned the feasibility of the model in consultations in which conflict occurs between patients and prescribers about the necessity of antibiotics for RTIs, and refers to delayed prescribing in this context as giving mixed messages in order for the GP to preserve his/her standpoint when an agreement can not be reached. Although agreement was the rule rather than the exception for the focus group GPs, Elwyn et al's critisism matches our findings.

With the "delegated authority"-perception in mind, the GPs inevitably had several requirements to the patient in order to issue delayed prescriptions, ie be "knowledgeable" and not demanding antibiotics for conditions not warranting their use.

The focus group GPs stated that delayed prescribing was well in line with what they saw as one of the principles of general practice; to find good solutions when facing practical challenges. The practical challenge in this setting was mainly that the patient consulted at a stage in the course of the condition where the indication for antibiotics could not be established, and the "good" in the solution of delayed prescribing was mainly to allow the patient to avoid the burden of a reconsultation. The questionnaire study confirms this, as 79% of the delayed prescriptions were issued because of "Uncertainty about indication for antibiotics" or "Difficulties with follow up".

We have described two main reasons for issuing delayed prescriptions, in addition to reducing antibiotics use: Arroll's *patient request for antibiotics*, which can be linked to the ethical principle of *respect for autonomy*, and Little's *safety netting*, which can be linked to the ethical principle of *beneficence*. As seen, our selection of GPs seem to be more pleased with a decision based on the principle of beneficence rather than the

principle of autonomy in this area. This may, as we have seen, been due to the GPs' experience that patient request for antibiotics is a minor challenge. One may also speculate that the ethical principles are weighted differently in different settings. A Scandinavian criticism of the ethical principle model is that autonomy is given too much weight at the expense of beneficence (108).

To conclude, delayed prescribing is generally regarded as an acceptable and practical strategy to reserve antibiotics for the cases for whom the GPs find them indicated. It is restricted to patients found capable of being delegated the authority to evaluate the indication for antibiotics after a certain amount of days. This capability depends on whether the patient shares the GPs views on prudent prescribing. If their views are not in line, delayed prescribing is still used, but to a smaller extent, and with less satisfied GPs.

GPs views on, and reasons to use, delayed prescribing seems to vary according to the GPs' setting. Researchers should evaluate this prior to educational interventions involving recommendation of delayed prescribing. There is a lack of knowledge on patients' views on and experiences with delayed prescribing. This should be explored in both high- and low antibiotics consuming settings.

GPs' use of delayed prescribing

Frequency

The focus group GPs stated that they had a set of requirements both to the patient, the situation and the clinical presentation in order to issue a delayed prescription, hence delayed prescribing was not seen as a strategy to be used in most cases of RTIs. This is reflected in the intervention study; only 11% of the patients given an antibiotic prescription for RTI, or 3% of all RTI patients, were given a delayed prescription.

In New Zealand, Arrol et al (62) found that GPs not exposed to any formal recommendation of delayed prescribing, reported that they would prescribe delayed prescriptions for a median of 10% of patients with upper RTI. Also, in a British questionnaire study (32), Edwards et al found that approximately 10% of RTI patients were given delayed prescriptions.

In the intervention study, 7.2% of the prescriptions for acute bronchitis were to be delayed. An observational study on delayed prescribing for acute cough in 14 primary care networks in 13 European countries (64) found that 11.8% of the patients that received a prescription received a delayed prescription. The rate for the participating Norwegian network was 6.6%, thus very close to our findings. Acute cough and acute bronchitis are not interchangeable categories, and participants in the observational study were not encouraged to use delayed prescribing. Nevertheless, a comparison with this study may indicate that the use of delayed prescribing is even more infrequent in Norway than in Europe as a whole. This may be related to the low antibiotic prescription rate in Norway; GPs in our setting may prefer a no-antibiotic option in cases where other GPs might prefer delayed or immediate antibiotics. In the Norwegian network, antibiotics were prescribed in 30% of the consultations, whereas the rate for all networks was 52.4%. Although old figures, antibiotic prescribing rates for URTIs in New Zealand has been found to be as high as 77.5% (109).

Also, GPs' limited use of delayed prescribing in the intervention study may be due to the relatively low patient demand – and GPs' perceived patient demand – for antibiotics in our setting. Both New Zealand and UK GPs report that patients generally expect antibiotics for RTI (36, 61), while our focus group GPs experienced that patients were happy to avoid antibiotics. In the questionnaire study, 52% of the patients reported that they expected the GP to prescribe antibiotics, compared to 65% in a corresponding British study (32). In a study from a large Norwegian emergency centre, as few as 38% of the patients consulting for RTIs reported that they expected antibiotics (110).

Diagnoses

One may ask if it is of importence to explore differences between the different RTI diagnoses. The British NICE guideline (26) advices are essentially common for all so called self-limiting RTI diagnoses. It has been hypothesised that sinusitis, URTI and acute bronchitis are variations of the same clinical condition (111). However, our studies show that the patients diagnosis is of great importance both when it comes to acceptability, prescribing and dispensing of delayed prescriptions.

The three studies were consistent regarding the most eligible diagnoses for delayed prescribing; acute sinusitis and acute otitis media. In the intervention study, 19.2% and 13.3% of the antibiotics were to be delayed for acute otitis media and acute sinusitis, respectively. In the broad category of URTI and RT symptoms, the corresponding rate was 16.3%. As discussed, this category is heterogenic. In absolute numbers, delayed prescriptions was most commonly issued for URTI and RT symptoms, followed by sinusitis, otitis and bronchitis.

Most studies on delayed prescribing are diagnosis-specific, hence there is a scarce basis of comparison for these findings. A small Canadian study (56) found a quite similar distribution; the most common condition which triggered delayed prescribing was URTI, followed by sinusitis, bronchitis, and pharyngitis. When examining which diagnoses have been tested in RCTs on delayed prescribing as a tool to lower antibiotics use (43), three trials are on acute otitis media, two on bronchitis/cough, one on common cold and one on sore throat. The reasons given for conducting these trials are generally that the specific condition is common in general practice, and that it often is treated with antibiotics, despite a marginal clinical effect. In one of the bronchitis trials, LRTI is said to be the most common condition treated in UK primary care, and that excess antibiotic prescribing in the US mainly is for this condition together with pharyngitis (51).

This seems not to be the case in Norway. There is no reason to believe that there are great differences between UK and Norway regarding the incidence of different RTIs. However, lay people's understanding of illnesses and their threshold to consult, as well as doctors' diagnostic labelling, may vary greatly between cultures and countries (112, 113). URTIs is by far the most common infectious condition in Norwegian primary care, and both this condition – despite a low antibiotic prescribing rate of 15.6% – and acute sinusitis generates more antibiotics prescriptions than bronchitis, which is at the same level as acute otitis (20). These factors may offer some explanation of the relatively high number of delayed prescriptions for URTI, otitis and sinusitis found in our studies.

Although sore throat was the object of the first trial on delayed prescribing (49), leading to much attention, only 5.6% of the patients receiving antibiotics for this

condition in the intervention study were instructed to delay. This may be related to the widespread use of StrepA point-of-care-test in Norwegian primary care (114). When in doubt, GPs probably let the test result guide the decision whether to prescribe (immediate) antibiotics or not, instead of issuing a delayed prescription.

The focus group GPs described characteristics of conditions suitable for delayed prescribing. First, it should have a certain, or at least a possible, bacterial etiology. Second, there should be an expectation that the indication for antibiotics would be established within a few days, dependent on the course of the condition. Both these characteristics match the understanding of acute sinusitis and acute otitis found in the Norwegian treatment guidelines for RTIs in primary care (87). Sinusitis and otitis are the only conditions in which the duration of symptoms determine whether antibiotics are indicated (seven days and one to three days, respectively). Even though the guidelines were not mentioned by our participants, they have to some degree been familiar with the content. Their preferral and relatively frequent use of delayed prescribing for sinusitis and otitis may be an indication that they used the strategy as a way to adhere to treatment guidelines.

Age

The focus group GPs did not express any strong opinions as to which age groups were most eligible for delayed prescriptions, apart from the notion that the eligible diagnosis of acute otitis mainly occurs in children. In the intervention study, children below 13 years had the highest delayed prescribing rate; more than 15% of the antibiotic prescriptions issued were to be delayed, while the corresponding rate for the age groups above 44 years were 4,6 – 8 %. In the logistic regression analysis, patients above 18 years had significantly lower odds of receiving antibiotics to be delayed compared to the reference age group of 0-6 years. In New Zealand, Arroll et al found that GPs generally restricted the use of delayed prescriptions to a particular age range, but they did not agree about what age range this should be.

Children differ from adults in several ways as regards to antibiotics use for RTIs. Even though children are prescribed more antibiotics than adults in primary care, antibiotic prescription rates are lower for children than for adults (20, 65), due to a

higher visit rate for children than for adults. This can partly explain the higher delayed prescribing rate among children found in our study; children may have milder symptoms than adults when visiting the GP, which may increase the GP's likelihood of instructing the parents to wait and see when issuing antibiotics. Second, the distribution of diagnoses in the different age groups obviously influences on the delayed prescribing rates for the corresponding age groups. Thirdly, the focus group GPs experienced that parents generally were sceptical about antibiotics, possibly increasing the likelihood of being prescribed delayed antibiotics for their children.

To conclude, even though being encouraged to use the strategy, GPs only adviced to delay 11% of their antibiotics prescriptions for RTI. The diagnoses found most suitable for delayed prescribing, were acute otitis and acute sinusitis; the only diagnoses for which symptom duration determines indication for antibiotics, according to Norwegian guidelines.

GPs should be encouraged to use delayed antibiotic prescribing as a tool to adhere to the current guidelines for antibiotic use in primary care. The adviced delay should correspond to the guidelines' recommended symptom duration determining indication for antibiotics, ie one – three days for acute otitis and seven days for acute sinusitis.

There is a lack of knowledge on the clinical outcome of delayed prescribing for acute sinusitis. This should be evaluated in a randomised controlled trial.

Patients' filling of antibiotic prescriptions

Our studies reports several different measurements on patients' filling of antibiotic prescriptions. The questionnaire study measures patients' self-reported filling and consumption of delayed antibiotics. The intervention study measures patients' filling of delayed and regular prescriptions, but also the filling of prescriptions issued in the baseline period, and by GPs in the control groups – hence prescriptions that are not defined as delayed or regular. First, we will discuss the latter.

Primary medication non-adherence, ie new medication not picked up, is normally seen as an unwanted phenomenon. There are wide variations in the reported

prevalence of primary non-adherence in different study settings, from 2.5% (115) to 35% (116). The appearance of e-prescriptions has made it easier to study primary non-adherence. In USA, Fischer et al (117) found that 72% of 82,245 e-prescriptions for new medications were filled, while the fill rate for antimicrobial drugs was 80%. In Sweden, Ax et al (115) found that as much as 97.5% of the prescriptions were filled, while 96.5% of the antibiotics were filled. Our baseline antibiotic-dispensing rate of 92.1% is towards the higher end of the spectre, close to the Swedish numbers. High antibiotic adherence rates in the Nordic countries have been commented earlier (104), without any conclusion. One may speculate whether this is related to the high levels of social and political trust found in the Nordic countries (118), which also implies trust in authorities such as doctors. Deschepper et al (119) have demonstrated a correlation between a country's antibiotic use and the country's score on the cultural dimension of Power distance. In countries with low Power distance, such as the Nordic countries, authority is based on rational arguments, and there is a high degree of equality between subordinates and superiors. A patient-doctor relationship characterised by trust and equality may result in high adherence.

Patients may have had a variety of reasons for not filling the 2775 (7.9%) prescriptions. A proportion may have been issued as delayed prescriptions. Also, the focus group GPs had a common experience that patients may delay or refuse antibiotic treatment on their own initiative, without the GP's advice (not reported in the paper). Certainly, some prescriptions also have been unclaimed unintendedly, ie due to leftovers, misunderstandings, oversight etc.

Consumption rates of antibiotics are considerably lower than dispensing rates. A meta-analysis found an overall antibiotics adherence rate of 62.2% (105), and a recent study on adherence to prescribed antibiotics for acute cough found adherence to at least a three-day course in only 57.8% of patients (104). The adherence rate varied across the different European networks participating in the study, with the highest rates being in the Scandinavian countries (Norway: 85.7%).

We found that both patients' age and diagnose influenced on the dispensing rate. Consistent with other studies, the dispensing rates were lowest in the youngest age groups (102, 115). Accordingly, GPs in the focus group study experienced that parents

commonly were sceptical about antibiotics. The diagnoses with the lowest dispensing rates were equivalent to the diagnoses found most eligible for delayed prescribing; sinusitis, otitis and URTI and RT symptoms. This indicates that the GPs to some extent used delayed prescribing for these conditions also prior to the intervention.

Filling of delayed prescriptions

The reported consumption rate for delayed prescriptions in the questionnaire study was 46%, and the dispensing rate in the intervention study was 59.2%. The latter is higher than any consumption rate reported in randomised controlled trials (RCTs) or surveys on delayed prescribing for RTIs (24% (53) – 53% (32)). There are several possible explanations for this high rate. The GPs in our study may have been less emphatic in delivering the wait-and-see advice to patients compared to GPs in RCTs or surveys on delayed prescribing. Also, the patients in our study were not aware that they were observed, hence there were no possibility of a social desirability bias. Furthermore, the patients in our study were given the delayed prescription at the time of their consultation, whereas in many of the delayed prescribing RCTs, patients had to return to their GP's office to pick up the prescription (50, 53, 54). The latter strategy results in lower consumption rates; 40% vs 28%, respectively. Finally, patients in our study may have filled the prescription for antibiotics but not consuming the medication. Figures from a British questionnaire study and our own questionnaire study show that respectively 15% (32) and 11% of patients stated that they did not consume the antibiotics, even though they had filled their delayed prescription. Applied to the intervention study, this corresponds to a 50–53% consumption rate.

Both in the questionnaire and the intervention study, delayed prescriptions were least likely to be filled in cases of otitis. This may be due to the natural course of this condition – approximately 80% of the cases of acute otitis in children results in a spontaneous recovery after a few days (24), whereas other RTIs may not have this sudden relief. Both studies also showed a clear association between age and prescription filling. In the questionnaire study, the adjusted odds ratio for reporting to consume antibiotics was 2,2 – 2,9 for the age groups above 16 years compared to the reference age group 0-16 years, while the intervention study showed a dispensing rate

of 66 – 94% for patients in the age groups above 44 years, and corresponding rates of 45 – 54% for patients below 19 years. Both parents scepticism towards antibiotics, the distribution of diagnoses in the different age groups and presumably milder symptoms among children may explain these differences.

To conclude, both delayed prescriptions and prescriptions not recorded as delayed or immediate, are most often unfilled among children, and in cases of acute sinusitis, acute otitis and URTI and RT symptoms. Hence, delayed prescribing's potential in decreasing antibiotics consumption is largest within these areas.

GPs should be aware of this, and also that only around half of the patients receiving delayed prescriptions in routine care will consume the antibiotics. GPs should take into account that a not negligible proportion of patients do not dispense their regular antibiotic prescriptions. For patients in dire need of treatment, GPs should take steps to assure that the patient adheres to the treatment plan. For other patients, this "appropriate non-adherence" should be both explored and utilised.

Effectiveness regarding lower antibiotics use

When tested in RCTs, delayed prescribing leads to a substantial reduction in consumed antibiotics (43). However, this is not to say that delayed prescribing has the same antibiotic saving potential when implemented in routine care. The effectiveness in routine care depends both on the patients' prescription filling in a setting where he/she is not aware of being observed, and whether the efforts to implement the strategy succeed. As to the first question, we have seen that approximately half of the delayed antibiotics will be consumed.

The remaining question is whether our efforts to implement delayed prescribing had an influence on the GPs behaviour. There has been a concern that implementing delayed prescribing will lead to more, rather than less, antibiotics consumption for RTIs. Although our focus group participants did not think it applied to them, some GPs mentioned that delayed prescribing might give a slippery-slope effect, leading patients to demand antibiotics for every RTI, thereby resulting in increased antibiotics consumption. In Peters and al's qualitative study from the UK (61), the participating

prescribers found it unlikely that delayed prescribing reduces antibiotic use. Others have shared this concern (50).

In our setting, this concern seems to be unjustified. The pop-up intervention GPs did not prescribe antibiotics more frequently than their controls; both groups issued antibiotics in 29,3% of the RTI consultations. Hence, it seems that when GPs are encouraged to use delayed prescribing, they replace immediate prescriptions with delayed prescriptions, rather than replacing a no-antibiotics option with delayed prescriptions. This was in line with the recommendations given as a part of the intervention. There are however two conditions to be taken into account when interpreting this result. First, the pop-up reminder was triggered upon issuing a prescription, hence it was first after the decision to prescribe that the GP was reminded on the delayed prescribing option. Second, the constant reminding of delayed prescribing may also have reminded the GP that their prescribing rate was registered, possibly influencing on this rate through the Hawthorn effect.

When introducing innovations to improve quality of care, the nature of the innovation must be taken into account. Incentives of change include the feasibility, credibility, accessibility and attractiveness of the innovation (28, 120). The focus group study stated that delayed prescribing is a method that suits well with the practice style and the way to do things in general practice. Many participants stated that they had come up with the idea of delayed prescribing early in their career, as a practical tool. This is in accordance with New Zealand findings (66). Others told that they had started using the strategy after hearing it recommended as part of the RxPAD study intervention. However, the credibility and attractiveness of the innovation were questioned by some of the GPs, and all agreed that delayed prescribing was feasible only to certain patients, under certain circumstances. Hence, we had no expectations of major changes in the participants use of delayed prescribing.

In terms of antibiotic-dispensing rates, we found no significant effect of the educational intervention. That is, the intervention did not seem to significantly increase participants' use of delayed prescribing. In the educational intervention, delayed prescribing was mainly advocated to GPs through passive dissemination of recommendations, ie a short lecture and a minor part of the group discussions. The

participants were not given details of their own use of delayed prescriptions and their patients fill rates, as they did with prescription rates and broad/narrow-spectrum prescription rates. Interventions using passive dissemination of recommendations alone have generally had little effect in changing physicians' behaviour (77).

The pop-up intervention produced a small but significant decrease in dispensing rate, indicating that the pop-up reminder increased the use of delayed prescribing. The absolute reduction in dispensing rate between the pop-up intervention group and the control group was 2.2%, and between the pop-up intervention group and the educational intervention 1.6%. A Cochrane review of on-screen, point-of-care computer reminders concludes that such interventions generally result in small to modest improvements in provider behaviour (121). In multifaceted interventions that aim to improve process adherence, the median effect of the computerised reminder alone was 1.9%, thus in line with our results.

Another way to interpret the effect of the intervention is to estimate the use of delayed prescriptions for the educational intervention control group and the pop-up intervention control group. Assuming that antibiotics to be taken immediately were dispensed in 94,3% of the cases and that delayed prescriptions were dispensed in 59.2% of the cases in all three groups, based on the figures from the pop-up intervention group, the delayed prescribing rate in the educational intervention control group would be 5,4% and in the pop-up intervention control group 7,1%, compared to 11% in the pop-up intervention group. Although these figures are based on assumptions, they suggest that the use of delayed prescribing might have doubled as a result of the interventions.

We have not found other intervention studies aimed at implementing delayed antibiotic prescribing in routine care. Six months after a Scottish RCT on delayed prescribing for acute cough (50), 68% of the recruiting GPs reported that they had continued to issue delayed prescriptions at least monthly. In Francis et al's comprehensive observational study on delayed prescribing for acute cough (64), GPs of the Southampton network more often issued delayed than immediate prescriptions. This network was linked to a university department that had conducted many studies of delayed prescribing. As it seems, GPs "forced" to issue delayed prescriptions due to

participation in trials, continue to use the strategy. However, this is not a feasible implementation strategy.

McDermott and co-workers (122) developed a computer-delivered intervention to promote the implementation of guidelines in general practice, including the NICE guidelines that recommends delayed prescribing for RTIs (26). As described in the Methods-section, the computerised pop-up software used in our intervention study was originally developed as a mere registration tool. Initially we did not set out to test whether this software was an implementation tool to recommend. Hence, no special efforts were put down in order to make the pop-up effective in influencing the GP to choose delayed rather than immediate prescribing; The pop-up window only contained a simple question on whether the prescribed antibiotic was a delayed or a regular prescription (Appendix E). This is clearly a disadvantage of the intervention study, and may partly explain the modest effect of the intervention. On the other hand, GPs may prefer computer-delivered interventions that are neutral and allow choice, as demonstrated by McDermott and co-workers (122). Also, as previously discussed, the effect of the pop-up reminder is in line with the effect found in other studies on computerised reminders.

As described in the Introduction section, there exists huge disagreements as to if delayed antibiotic prescribing should be promoted at all. The authors of the Cochrane review on delayed prescribing (43) seem to find no reasons to recommend the strategy. They conclude that when the GP feels that it is safe not to prescribe antibiotics immediately, no – rather than delayed – antibiotics will give the best result; the same level of clinical outcomes and patient satisfaction as delayed prescribing, but lower antibiotic consumption. Still, the NICE guidelines on antibiotic prescribing for RTIs in primary care (26) recommend delayed prescribing as an equally good option as no prescribing in RTI cases where the patient is not at risk of developing complications. Our studies were carried out within the setting of an educational intervention study mainly aiming at a no antibiotics option, according to the Norwegian guidelines on the treatment of RTIs in general practice. In this setting, efforts to implement delayed antibiotic prescribing did not seem to weaken the no antibiotics recommendation. This demonstrates that there is a niche for delayed

prescribing as an antibiotic saving strategy, forming a middle ground between the Cochrane review conclusion and the NICE guidelines: A no antibiotics option is to be preferred for RTI patients who do not need antibiotics immediately. Delayed antibiotics is the second choice, and is suitable especially for conditions in which symptom duration is of importance regarding indication for antibiotics.

To conclude, promoting delayed prescribing for RTIs in routine care results in decreased antibiotics dispensing, without any increased antibiotic prescribing. Given the relatively small absolute effect of the combined educational- and pop-up intervention on dispensing rate, we do not recommend this as an intervention to be used alone. However, as a part of multi-faceted interventions to decrease antibiotics prescribing for RTIs, strategies to increase the use of delayed prescriptions seem to give an additional effect in decreasing dispensed, and thereby consumed, antibiotics. When advocating delayed prescribing, this should allways be accompanied by a firm message that no antibiotics is the preferred option for RTIs that do not fill the requirements of immediate antibiotics at the time of the consultation.

Researchers should evaluate the effect and the cost-effectiveness of other interventions to promote delayed prescribing, both in low- and high antibiotics consuming settings.

Conclusion

In conclusion, this thesis suggests that

- GPs find delayed prescribing an acceptable strategy for reserving antibiotics to the cases where it turns out to be medically indicated, according to current treatment guidelines.
- GPs have strict requirements as to which patients, for which diagnoses and in which situations they will issue delayed prescriptions, resulting in an infrequent use of the strategy.
- Delayed prescribing is less effective in reducing antibiotics use in routine care than in a trial setting, but still only about half of the delayed antibiotics will be consumed.
- The strategy's potential in reducing antibiotics use is largest in cases of acute otitis and acute sinusitis.
- Efforts to promote delayed prescribing give a small decrease in dispensed antibiotics, without any accompanying increase in prescribed antibiotics.

The messages to health authorities, postgraduate GP teachers and other entities working to promote prudent antibiotics use are:

- The use of delayed prescribing as a tool to adhere to treatment guidelines should be encouraged, especially in cases of acute otitis and acute sinusitis.
- A computerised pop-up reminder on delayed prescribing is not recommended as a sole intervention, but should be considered as an element in multi-faceted interventions.
- When promoting delayed prescribing, this should always be accompanied by a firm message stating that no antibiotics is the preferred option for RTIs which do not fill the requirements of immediate antibiotics at the time of consultation.
- The antibiotics saving potential of delayed prescribing seems to be low in our setting. This potential should be explored before deciding whether to promote the strategy in new settings.

Future research

Our study suggests that there is need for research which:

- Evaluates the clinical outcome of delayed versus immediate and no antibiotics prescribing for acute sinusitis in a randomised controlled trial.
- Explores patients' non-adherence to antibiotics, in order to produce knowledge on how and whether this non-adherence can be utilised to decrease antibiotics use.
- Evaluates the effect and the cost-effectiveness of interventions to promote delayed prescribing in various settings.
- Evaluates the effect and the cost-effectiveness of interventions to promote delayed prescribing using various intervention elements.
- Explores patients' views on and experiences with delayed prescribing in both high and low antibiotics consumption settings.

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Paper I

Høye S, Gjelstad S, Lindbæk M.

Effects of interventions to promote delayed prescribing for respiratory tract infections on antibiotic-dispensing rates.

Provisionally accepted, Br J Gen Pract.

Paper II

Høye S, Frich JC, Lindbæk M.

Delayed prescribing for upper respiratory tract infections: a qualitative study of GPs' views and experiences.

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Paper III

Høye S, Frich JC, Lindbæk M.

Use and feasibility of delayed prescribing for respiratory tract infections: A questionnaire survey.

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Use and feasibility of delayed prescribing for respiratory tract infections: A questionnaire survey

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Abstract

Background: Delayed prescribing of antibiotics for respiratory tract infections (RTIs) lowers the amount of antibiotics consumed. Several national treatment guidelines on RTIs recommend the strategy. When advocating treatment innovations, the feasibility and credibility of the innovation must be taken into account. The objective of this study was to explore GPs use and patients uptake of wait-and-see prescriptions for RTIs, and to investigate the feasibility of the strategy from GPs' and patients' perspectives.

Methods: Questionnaire survey among Norwegian GPs issuing and patients receiving a wait-and-see-prescription for RTIs. Patients reported symptoms, confidence and antibiotics consumption, GPs reported diagnoses, reason for issuing a wait-and-see-prescription and their opinion about the method.

Results: 304 response pairs from consultations with 49 GPs were received. The patient response rate was 80%. The most common diagnosis for the GPs to issue a wait-and-see prescription was sinusitis (33%) and otitis (21%). 46% of the patients reported to consume the antibiotics. When adjusted for other factors, the diagnosis did not predict antibiotic consumption, but both being 16 years or more (p = 0,006) and reporting to have a fever (p = 0,012) doubled the odds of antibiotic consumption, while feeling very ill more than quadrupled the odds (p = 0,002). In 210 cases (69%), the GP found delayed prescribing a very reasonable strategy, and 270 patients (89%) would prefer to receive a wait-and-see prescription in a similar situation in the future. The GPs found delayed prescribing very reasonable most frequently in cases of sinusitis (79%, p = 0,007) and least frequently in cases of lower RTIs (49%, p = 0,002).

Conclusion: Most patients and GPs are satisfied with the delayed prescribing strategy. The patients' age, symptoms and malaise are more important than the diagnosis in predicting antibiotic consumption. The GP's view of the method as a reasonable approach depends on the patient's diagnosis. In our setting, delayed prescribing seems to be a feasible strategy, especially in cases of sinusitis and otitis. Educational efforts to promote delayed prescribing in similar settings should focus on these diagnoses.

Background

General practitioners (GPs) issue more than 90% of antibiotic prescriptions in Norway, and about 60% of these are issued for common respiratory tract infections (RTIs) [1]. RTIs are often self-limiting, and antibiotics have a modest role in the treatment of such conditions [2]. Unnecessary use of antibiotics is a global concern, as it leads to antibiotic resistance, adverse drug reactions, and medicalization of self-limiting disease. Antibiotic prescription rates are relatively low in Norway and other Northern European countries [3], but a recent Norwegian prescription study found that there still is room for improvement [4].

Much effort has been put into developing strategies to reduce over-consumption of antibiotics for RTIs in general practice, and randomized controlled trials have provided evidence for delayed prescribing as an effective strategy. Reported pick up rates for wait-and-see prescriptions varies from 24 - 38% (otitis media) [5,6], 31%

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(sore throat) [7], 20 - 45% (cough) [8,9], to 48% (common cold) [10]. The safety of the method seems to be good, and there is probably no increase in complication rates, but a longer duration of certain symptoms in some studies [11].

It has been argued that delaying antibiotics has little advantage over avoiding them where it is safe to do so [11]. However, the question regarding safety in handling RTIs is not clear cut, and factors like physician insecurity, patient demands and work load lead GPs to prescribe antibiotics without a good medical indication [12]. GPs experience numerous situations where they find delayed prescribing reasonable [13]. Hence, delayed prescribing might have an important place in the management of RTIs [14]. The strategy is recommended in several national treatment guidelines on RTIs in general practice [15-17], and it is part of the intervention in quality improvement studies on appropriate antibiotics prescribing [18-20].

Delayed prescribing is not universally endorsed by GPs [13,21], though patients seem to be confident and satisfied with wait-and-see prescriptions [7,22]. When advocating treatment innovations to improve quality of care, the feasibility and credibility of the innovation must be taken into account [23]. There is a lack of knowledge on if, and in which situations, GPs find delayed prescribing a reasonable approach, and in which situations GPs choose to use the strategy.

The aim of this study is to explore GPs use and patients uptake of wait-and-see prescriptions for RTIs, and to investigate the feasibility of the strategy from GPs' and patients' perspective.

The terms "delayed prescribing" and "wait-and-see prescription" are used synonymously in the literature. In this paper we use "delayed prescribing" for the strategy, and "wait-and-see prescription" denotes the prescription itself.

Methods

Subjects and setting

We translated and adopted a questionnaire on patients' response to delayed prescription used in a previous study [22], and developed a questionnaire on GPs reasons for issuing wait-and-see prescriptions.

The study was conducted as a part of the Prescription Peer Academic Detailing (Rx-PAD) Study, a cluster-randomized educational intervention study in Norwegian general practice with the aim of improving antibiotic prescribing in respiratory tract infections [18]. The elements of the intervention were educational outreach visits to the participants' continuing medical education groups comprising presentation and discussion of evidence-based antibiotics prescribing for RTIs, collection of individual prescription data, audit based on individual feedback reports, as well as a one-day regional seminar. As part of the seminar, one of the authors (SH) gave a lecture on the evidence regarding delayed prescribing, and invited the GPs to recruit patients to the present study. 58 GPs agreed to participate. In addition, 16 GPs affiliated to the Department of General Practice, University of Oslo, were given the same lecture, and agreed to participate (Figure 1).

Eligible patients were those of any age who consulted the GP for a RTI, and to whom the GP found it appropriate to offer a wait-and-see prescription. In the course of the consultation, the GP handed the patient an antibiotic prescription together with a patient questionnaire, a consent form, an information leaflet and a pre-stamped envelope. The patient was instructed to wait for a certain amount of time, chosen by the GP, before deciding whether to take the antibiotics or not. The questionnaire was to be filled once the patient had made this decision. After the consultation, the doctor filled in the GP questionnaire. Patients were rewarded with a scratchcard upon responding, while the GP would receive a gift card for a CD when they had recruited 10 patients. Recruitment took place during April 2006 through June 2008.

The Regional Committee for Research Ethics in Oslo, Norway, approved the study (S-05272).

Statistical analysis

Chi square test was used to compare those patients who reported to consume antibiotics and those who did not, with regard to both patient factors (demographic characteristics, presenting symptoms, expectations, confidence in deciding whether to use the prescription) and GP factors (diagnose, reason for giving wait-and-see prescription, reasonableness, and impression of expectations and use of the prescription). Logistic regression analysis was performed with the dependent variable being whether the patient reported to consume the antibiotics or not. Further, we compared cases where the GP found delayed prescribing very reasonable and cases where where the GP did not. A significance level of 5% was applied. Analyses were performed using SPSS 14 and 18.

Material

Out of a total of 68 GPs, 49 (72%) recruited on average 8.5 patients each (median 6; span 1-34). 19 (28%) GPs recruited no patients. We received 413 responses from GPs and 332 responses from patients. Five patients informed that they did not want to participate, and consequently we removed the corresponding GPs responses. For five of the patient responses, we did not receive a corresponding GPs response, resulting in 327 response pairs and a patient response rate of 80%.

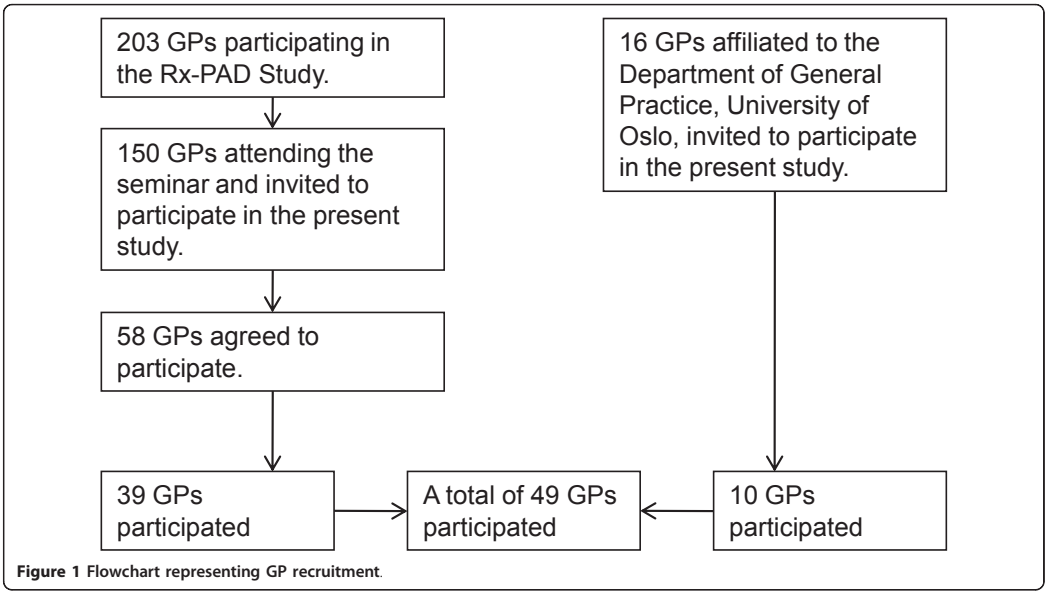

Figure 1 Flowchart representing GP recruitment.

17 response pairs were excluded because the GPs had included patients who were treated for other conditions than RTIs, and an additional six response pairs were excluded because the patients failed to answer whether they had taken antibiotics. 304 response pairs remained for analysis.

We grouped diagnoses according to previouos studies on RTIs [1,24]. Table 1 displays the characteristics of the participating patients and GPs.

Table 1 Characteristics of participating patients and GPs

	n	(%)
Patients	304	(100)
Gender		
Female	204	(67)
Male	100	(33)
Grouped age (years)		
Less than 16	100	(33)
16-59	180	(59)
60 and over	24	(8)
GPs	49	(100)
Gender		
Female	13	(27)
Male	36	(73)
Delayed prescriptions issued		
1-4 prescriptions	19	(39)
5-9 prescriptions	12	(24)
10-19 prescriptions	13	(27)
More than 20 prescriptions	5	(10)

Results

Comparison of responders and non-responders

Of the 81 non-responding patients, there were significantly more men (47% vs 33%) and more patients with upper RTIs (34% vs 20%), compared to the group of responders.

Delayed prescribing - when and why

Table 2 shows the diagnoses given by the GPs when issuing a wait-and-see prescription, and the diagnose groups used in the further analysis. In comparison with a reference material of antibiotic prescribing for respiratory tract infections in a Norwegian county during two winter months in 2003, our material shows an overrepresentation of sinusitis (33,2% vs 14,6%) and otitis (21,4% vs 9,1%), and an underrepresentation of lower RTI (13,5% vs 28,5%) and tonsillitis (7,9% vs 16,8%).

The majority (58%) of the children given a wait-and-see-prescription had otitis, while the majority (49%) of adults had sinusitis, and the elderly had lower RTI (46%). Patients with the diagnosis of upper RTI reported feeling more ill (p = 0,009), and patients with tonsillitis felt less ill (p = 0,04) compared to patients with other diagnoses.

The GPs reported that they issued wait-and-see prescriptions mainly because of uncertainty about the indication for antibiotics (211 cases, 69%) or uncertainty about the diagnose (32 cases, 11%). (See also table 4). Difficulties connected to follow up was given as reason in 29 cases (10%), and disagreement with the patient on

Table 2 Diagnoses where GPs issued delayed prescription, compared to a reference material of antibiotic prescriptions for respiratory tract infections

						Reference (Vestfold study)	
Diagnose group	Diagnose	ICPC-2 code	n	%	(95% CI)	%	(95% CI)
Upper respiratory tract symptoms and infections			**60**	**19,7**	**(15,3-24,2)**	**21,3**	**(20,0-22,6)**
	Cough	r05	6				
	Sinus symptom/complaint	r09	7				
	Throat symptom/complaint	r21	4				
	Upper respiratory infection acute	r74	43				
Lower respiratory tract infections			**41**	**13,5**	**(9,7-17,3)**	**28,5**	**(27,1-29,9)**
	Acute bronchitis/bronchiolitis	r78	36				
	Pneumonia	r81	4				
	COPD	r95	1				
Ear infections			**65**	**21,4**	**(16,8-26,0)**	**9,1**	**(8,2-10,0)**
	Ear pain/earache	h01	1				
	Ear discharge	h04	1				
	Ear symptom/complaint other	h29	1				
	Acute otitis media/myringitis	h71	62				
Sinusitis			**101**	**33,2**	**(27,9-38,5)**	**14,6**	**(13,5-15,7)**
	Sinusitis acute/chronic	r75	101				
Acute tonsillitis			**24**	**7,9**	**(4,9-10,9)**	**16,8**	**(15,7-18,0)**
	Strep throat	r72	5				
	Tonsillitis acute	r76	19				
Other respiratory diagnoses			**13**	**4,3**	**(2,0-6,6)**	**9,7**	**(8,8-10,6)**
	Laryngitis/tracheitis acute	r77	4				
	Influenza	r80	7				
	Respiratory infection other	r83	2				

the need for antibiotics in 12 cases (4%). In 44 cases (14%), the GP reported "Other reasons", and in 34 of these cases, this was the only explanation for issuing the wait-and-see prescription. "Other reasons" were in all but one case described as clinical or therapeutic peculiarities in the specific situation (eg. mild symptoms, pregnancy, short duration of symptoms, other treatment started).

Factors associated with the decision to consume antibiotics

141 (46%) of the patients reported to consume the antibiotics. Diagnoses and patients' factors associated with consumption of antibiotics are presented in table 3. There were no statistically significant differences between those who reported to have consumed antibiotics and those who did not in respect of their gender or their educational level.

Patients diagnosed with an ear infection were less likely to consume antibiotics. Patients younger than 16 years were less likely to consume antibiotics (p = 0,04). When reporting to have fever, patients were more likely to consume antibiotics (p = 0,012). Also, a higher number of reported symptoms (p = 0,024) and more malaise (p = 0,012) made patients more likely to consume antibiotics.

The prognostic variables in table 3 resulting in a p-value of 0,25 or less were included in a logistic regression analysis, together with the background characteristics age, gender and educational level, the dependent variable being whether the patient reported to consume the antibiotics or not (Table 4). Symptom sum was not included, as this variable was closely correlated to, and also included, the individual symptoms. Four factors were significantly associated with consuming antibiotics. Having a fever, reporting to be very ill and being of older age increased the odds, while a nasal congestion decreased the odds of consuming antibiotics.

When asked whether they thought the patient would take the antibiotics, the GPs answered yes in 51 (17%) of the cases, no in 131 (43%) of the cases and that they were uncertain in 122 (40%) of the cases. The GPs' presumption was slightly correlated with the patients' reported action (p = 0,025, correlation coefficient 0,166).

Feasibility of delayed prescribing

262 (86%) out of the 304 patients stated that they felt confident in deciding whether to use the prescription,

Table 3 Patients' characteristics, presenting symptoms and expectations, by consumption of antibiotics

	Total (%)		Patients who took antibiotics (%)[a] (n = 141)		Patients who did not take antibiotics (%)[a] (n = 163)		Pick up rate %	P-value [b]
Grouped age (years) n = 304								
Less than 16	100	(33)	38	(27)	62	(38)	38	0,04*
16-59	180	(59)	90	(64)	90	(55)	50	0,13
60 and over	24	(8)	13	(9)	11	(7)	54	0,43
Gender n = 304								
Female	204	(67)	95	(67)	109	(67)	47	0,93
Male	100	(33)	46	(33)	54	(33)	46	
Highest education n = 302 (140/162)								
Basic education (7-9 years)	34	(11)	15	(11)	19	(12)	44	0,78
High school (10-12 years)	105	(35)	50	(36)	55	(34)	48	0,75
College/university (>12 years)	163	(54)	75	(53)	88	(54)	46	0,9
Presenting symptoms n = 303 (141/162)								
Sore throat	101	(33)	52	(37)	49	(30)	51	0,21
Earache	94	(31)	40	(28)	54	(33)	43	0,37
Cough	124	(41)	63	(45)	61	(37)	51	0,2
Fever	111	(37)	62	(44)	49	(30)	56	0,012*
Sinus pain	118	(39)	56	(40)	62	(38)	47	0,76
Muscular aches	32	(11)	17	(12)	15	(9)	53	0,42
Runny nose	49	(16)	22	(16)	27	(17)	45	0,82
Nasal congestion	94	(31)	39	(28)	55	(34)	41	0,25
Malaise	72	(24)	38	(27)	34	(21)	53	0,21
Wheezing/shortness of breath	61	(20)	31	(22)	30	(18)	51	0,44
Other symptoms	17	(6)	10	(7)	7	(4)	59	0,29
Sum symptoms	873		430 (3,05 pr case)		443 (2,73 pr case)			
1 symptom	87	(29)	30	(21)	57	(35)	34	0,008*
2-4 symptoms	161	(53)	81	(57)	80	(49)	50	0,15
More than 4 symptoms	55	(18)	30	(21)	25	(15)	55	0,18
Feeling ill n = 301 (139/162)								
Very ill	34	(11)	24	(17)	10	(6)	71	0,003*
Modestly ill	193	(64)	89	(64)	104	(64)	46	0,9
A bit ill	74	(25)	26	(19)	48	(30)	35	0,026*
Patient expectations n = 303 (141/162)								
Antibiotic prescription	157	(52)	79	(56)	78	(48)	50	0,16
Other prescription	44	(15)	20	(14)	24	(15)	45	0,89
Advice	51	(17)	22	(16)	29	(18)	43	0,61
Tests	144	(48)	69	(49)	75	(46)	48	0,61
Referral	9	(3)	3	(2)	6	(4)	33	0,43
Sicknote	43	(14)	24	(17)	19	(12)	56	0,18
No expectations	50	(17)	19	(13)	31	(19)	38	0,19
Diagnosis group n = 304								
Upper respiratory tract symptoms and infections	60	(20)	34	(24)	26	(16)	57	0,075
Lower respiratory tract infections	41	(14)	21	(15)	20	(12)	51	0,5
Ear infections	65	(21)	23	(16)	42	(26)	35	0,045*
Sinusitis	101	(33)	47	(33)	54	(33)	47	0,97
Acute tonsillitis	24	(8)	11	(8)	13	(8)	46	0,96
Other respiratory diagnoses	13	(4)	5	(4)	8	(5)	38	0,56

a Percentages within the brackets are those within the patient group.

b Pearson chi-square.

Table 4 Logistic multivariate regression analysis

	Unadjusted		Adjusted [a]	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age (years)				
Less than 16	1		1	
16-60	1,63 (0,99 - 2,69)	0,054	2,21 (1,25 - 3,92)	0,006
60 and over	1,93 (0,79 - 4,74)	0,15	2,89 (1,01 - 8,29)	0,048
Sex				
Male	1		1	
Female	1,02 (0,63 - 1,65)	0,93	0,80 (0,47 - 1,36)	0,41
Highest education				
Basic education (7-9 years)	1		1	
High school (-12 years)	1,15 (0,53 - 2,51)	0,72	1,19 (0,50 - 2,84)	0,7
College/university (>12 years)	1,08 (0,51 - 2,27)	0,84	1,33 (0,58 - 3,05)	0,5
Symptoms [b]				
Sore throat	1,36 (0,84 - 2,19)	0,21		
Cough	1,35 (0,85 - 2,14)	0,2		
Fever	1,83 (1,14 - 2,93)	0,012	1,94 (1,15 - 3,27)	0,012
Nasal congestion	0,75 (0,46 - 1,23)	0,25	0,58 (0,34 - 0,99)	0,046
Malaise	1,4 (0,82 - 2,38)	0,21		
Feeling ill				
A bit ill	1		1	
Modestly ill	1,58 (0,91 - 2,75)	0,11	1,46 (0,81 - 2,61)	0,21
Very ill	4,43 (1,84 - 10,67)	0,001	4,55 (1,77 - 11,75)	0,002
Patient expectations [b]				
Antibiotic prescription	1,39 (0,88 - 2,18)	0,16		
Sicknote	1,56 (0,81 - 2,98)	0,18		
No expectations	0,66 (0,36 - 1,24)	0,2		
Diagnosis group				
Sinusitis	1			
Lower respiratory tract infections	1,21 (0,58 - 2,5)	0,61		
Otitis	0,63 (0,33 - 1,2)	0,16		
Upper respiratory tract symptoms and infections	1,5 (0,79 - 2,86)	0,22		
Tonsillitis	0,97 (0,4 - 2,38)	0,95		
Other	0,72 (0,22 - 2,35)	0,58		

Odds ratio for reporting to consume the antibiotics.

a The odds ratios are adjusted for the background characteristics and for the other surviving variables in the model.

b The reference value is *not* having the spesific symptom/expectation.

12 patients (4%) felt unconfident, and the remaining 30 patients (10%) felt neither. There were no significant correlations between confidence and certain diagnosis or prescription pick up rate. 270 patients (89%) would prefer to receive a wait-and-see prescription in a similar situation in the future, nine patients (3%) would prefer not to be offered delayed prescribing, whereas 24 patients (8%) were uncertain what they preferred. Patients with upper RTI did to a lesser extent wish for delayed prescribing in the future (48/60, 80%, p = 0,016).

Out of the 163 patients stating not to consume the antibiotics, 64 (39%) reported to have saved the prescription or the medication for later.

In 210 (69%) of the cases, the GPs answered that they viewed delayed prescribing a very reasonable approach in the specific clinical setting. In 90 cases (30%) they found the approach fairly reasonable, and in four cases (1%) they expressed to be uncertain on this subject. Table 5 presents factors associated with GPs finding delayed prescribing a reasonable strategy.

12 wait-and-see prescriptions from 10 different GPs were issued because of disagreement with the patient. In three of these cases (25%), the GP found the method very reasonable, as opposed to 71% when the wait-and-see prescription was issued for other reasons.

In sinusitis, the GPs found delayed prescribing very reasonable in 79% of the cases. At the opposite, the GPs

Table 5 GPs opinion of delayed prescribing as a reasonable strategy

	Total (%)		Wait-and-see Rx very reasonable (%) (n = 210)		Wait-and-see Rx not very reasonable (%) (n = 94)		Very reasonable %	P-value [a]
Diagnosis group n = 304								
Upper respiratory tract symptoms and infections	60	(20)	35	(17)	25	(27)	58	0,044*
Lower respiratory tract infections	41	(14)	20	(10)	21	(22)	49	0,002*
Ear infections	65	(21)	50	(24)	15	(16)	77	0,12
Sinusitis	101	(33)	80	(38)	21	(22)	79	0,007*
Acute tonsillitis	24	(8)	17	(8)	7	(7)	71	0,85
Other respiratory diagnoses	13	(4)	8	(4)	5	(5)	62	0,55
GP's reason for giving delayed prescription n = 304								
Uncertainty about indication for antibiotics	211	(69)	151	(72)	60	(64)	72	0,16
Other reason	44	(14)	34	(16)	10	(11)	77	0,2
Uncertainty about diagnose	32	(11)	22	(10)	10	(11)	69	0,97
Difficulties with follow up	29	(10)	19	(9)	10	(11)	66	0,66
Disagreement with the patient	12	(4)	3	(1)	9	(10)	25	0,001*
GP's expectation n = 304								
Patient is likely to take antibiotics	51	(17)	29	(14)	22	(23)	57	0,039*
Patient is not likely to take antibiotics	131	(43)	100	(48)	31	(33)	76	0,017*
Uncertain	122	(40)	81	(39)	41	(44)	66	0,41
GP's impression of patient's antibiotics expectation n = 303 (209/94)								
Patient expected antibiotics	73	(24)	47	(22)	26	(28)	64	0,32
Patient did not expect antibiotics	150	(50)	104	(50)	46	(49)	69	0,93
Uncertain	80	(26)	58	(28)	22	(23)	73	0,44
Grouped age (years) n = 304								
Less than 16	100	(33)	69	(33)	31	(33)	69	
16-59	180	(59)	124	(59)	56	(60)	69	0,98
60 and over	24	(8)	17	(8)	7	(7)	71	
Gender n = 304								
Female	204	(67)	139	(66)	65	(69)	68	0,61
Male	100	(33)	71	(34)	29	(31)	71	

a Pearson chi-square.

found the method very reasonable in 49% of the lower RTI-cases. The GPs found delayed prescribing more reasonable when they thought the patient would not fill in the prescription (p = 0.017).

Discussion

Summary of main findings

General practitioners who have been informed about the use of wait-and-see prescriptions in RTIs, most often use the strategy in cases of acute sinusitis and acute otitis media. These are also the diagnoses for which the GPs find the strategy most reasonable. The reported reason for issuing a wait-and-see prescription is most commonly uncertainty about indication for antibiotics.

Patients receiving a wait-and-see prescription are confident in the decision whether to start taking the medication, and half of the patients report to consume the antibiotics. Feeling very ill, having fever, and being more than 16 years predict consumption of antibiotics, while reporting nasal congestion is negatively associated with consuming antibiotics.

Comparison with existing litterature

To our knowledge, this is the first survey on delayed prescribing in which different diagnoses are compared, and in which the feasability of the strategy among GPs is measured.

We found that GPs issue wait-and-see prescription most commonly in sinusitis and otitis. When compared to a similar group of GPs in Norway [4], our numbers show an over-representation of sinusitis and otitis, which indicates that patients receiving antibiotics for otitis or sinusitis more often will be instructed to wait than patients receiving antibiotics for other conditions. This may be because otitis and sinusitis are the two conditions for which the Norwegian National Treatment Guidelines recommend "watchful waiting" [16]. A Norwegian prescription study shows that tonsilitis is the

diagnosis that would most often warrant a prescription for antibiotics, while URTI is at the other extreme [4]. This may explain why patients with tonsilitis in our study felt less ill, and patients with URTI felt more ill, as one could assume that the moderately ill patients with tonsilitis would be given an immediate prescription for antibiotics, and the moderately ill patients with URTI would not be given antibiotics at all.

The first evidence on the advantages of delayed prescribing came from studies on patients with sore throat in the United Kingdom in 1997 [7], and the spreading of this evidence is considered as one of the reasons why antibiotic consumption continued to decrease in the UK from the late 1990s and onwards [25]. However, in our study sore throat is not a condition in which the GPs readily give wait-and-see prescriptions. This may be due to the widespread use of point-of-care streptococcal throat tests in Norwegian general practice [26], and that the GPs let the test results decide whether to prescribe antibiotics.

In our study, 46% of the patients reported to consume the antibiotics and 86% reported confidence in deciding whether to take the antibiotics. These findings are similar to Edwards et al, who in a comparable British study [22] found a consumption rate of 53%, and 87% confident patients. In both studies, fever was found as a predictor for consuming antibiotics. Fever is shown to be the most important cue when parents take treatment decisions on behalf of their sick child [27].

There were some interesting differences regarding patient expectations. Fewer patients in our study expected antibiotics (52%) compared to the findings of Edwards et al (65%). This may be due to a real difference in antibiotic expectation, despite similar antibiotic prescription rates in the two countries [3]. Another explanation may be that the GPs in our study to a lesser degree used delayed prescribing as a tool to meet patient expectation for antibiotics. Substantially more patients in our setting expected tests or referral (50% vs Edwards et al: 2%). This indicates that the more widespread use of point-of-care tests in our setting compared to Edwards et al's UK setting [28] has had an influence on patients' expectations.

We found differences in reported consumption rates for the various diagnoses, and the internal variation shows some resemblence with the results achieved in various diagnose-specific RCTs on delayed prescribing; 35% vs 24 - 38% (otitis media) [5,6], 46% vs 31% (sore throat) [7], 51% vs 20 - 45% (lower RTI/cough) [8,9], and 57% vs 48% (upper RTI/common cold) [10]. The results are understandably not directly comparable, as the methods of issuing delayed prescriptions differ between various studies, the diagnostic criteria varies, and the antibiotic prescription rates [3] and the patients' views on respiratory tract infections show great variance between countries [29]. Nevertheless, the variance between diagnose groups in our study may give valuable information as the prescriptions for various conditions were given in the same setting.

The natural course of otitis in children is a spontaneous recovery after a few days in approximately 80% of the cases [30], whereas other RTIs may not have this sudden relief. This might explain why ear infection is the diagnose with the lowest pick up rate.

The overall satisfaction with delayed prescribing was high both among GPs and patients. GPs consider overuse of antibiotics a problem [31], and may feel uncomfortable prescribing antibiotics [32]. Thus, there is no surprise that GPs in our study found wait-and-see prescriptions most reasonable among patients who they thought would not pick it up.

Although small numbers, our findings suggest that GPs find delayed prescribing more reasonable in situations of clinical uncertainty rather than in situations where patients demand antibiotics, which is in accordance with the findings in a previous, qualitative study among a similar group of GPs [13].

The GPs found delayed prescribing most reasonable in cases of otitis and sinusitis while the strategy was less valued in cases of upper and lower respiratory tract infections. This may also, as suggested above, be due to the difference in the current understanding and recommended treatment of the various conditions; indication for antibiotics in otitis and sinusitis depends partly, according to Norwegian guidelines, on the duration of symptoms. When it comes to bronchitis and URTI/common cold, the main recommendation is to avoid antibiotics altogether. This might explain why these diagnoses were found less appropriate for delayed prescribing.

Strengths and limitations

The response rate (80%) was relatively high in comparison to a previous study [22]. The aim of this study was not to explore clinical outcomes and safety of the delayed prescribing strategy, and potential differences in treatment outcomes for different diagnoses have not been investigated.

This study does not allow to directly compare the use of wait-and-see prescriptions with the use of prescriptions for antibiotics to be taken immediately, since we have no record of the latter. For illustrative means, we have compared our findings with a reference material of antibiotic prescriptions for RTIs during two winter months.

The participating GPs had agreed to take part in a study on delayed prescribing, and they might hold a more positive view towards the strategy compared to the relatively large group of invited GPs who did not

participate. However, both high and low prescribers of wait-and-see-prescriptions were represented.

As in all questionnaire surveys, our results depend on the respondents report, and not necessarily on their action. The patient questionnaire and information leaflet were carefully constructed to avoid an impression that not picking up the prescription would be the preferred solution, so as to minimize a desirability bias. Still, the reported antibiotics consumption rate of 46% may be a underreporting of what actually happened.

The diagnoses referred in this study are the ones chosen by the GPs. We do not know if, and to what extent, diagnostic criteria were followed, and the diagnostic accuracy may have varied between the different GPs.

Conclusion

Most patients and GPs are satisfied with the delayed prescribing strategy. The patients' age, symptoms and malaise are more important than the diagnosis in predicting antibiotic consumption. The GP's view of the method as a reasonable approach depends on the patient's diagnosis. In our setting, delayed prescribing seems to be a feasible strategy, especially in cases of sinusitis and otitis. Educational efforts to promote delayed prescribing in similar settings should focus on these diagnoses.

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Authors' contributions

SH and ML conceived and designed the study. SH collected and analysed the data and wrote the draft manuscript. All authors interpreted the data, critically revised the draft for important intellectual content, prepared the manuscript, and gave final approval of the version to be published.

Authors' information

ML edited and SH took part in developing the Norwegian National guidelines for antibiotic use in primary health care 2008.

Competing interests

The authors declare that they have no competing interests.

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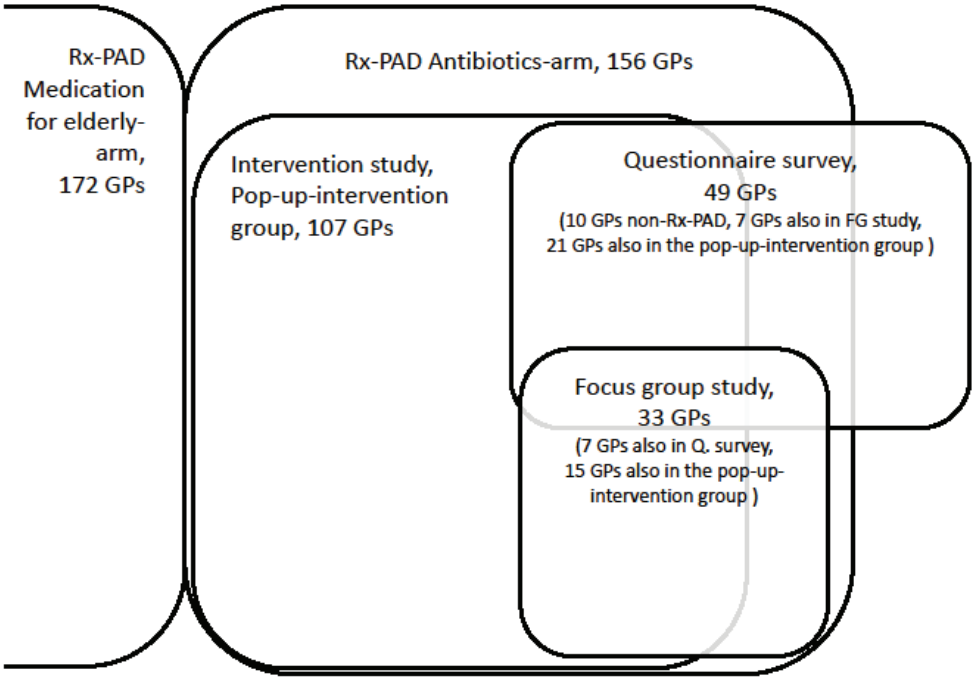
Appendix A – Participating GPs



Appendix B – Focus group interview guide

Do you use wait-and-see prescriptions? Why/why not?

Which patients do you offer wait-and-see prescriptions?

For which diagnoses do you use wait-and-see prescriptions?

In what situations do you use wait-and-see prescriptions?

Which advantages / disadvantages do you experience with wait-and-see prescriptions?

What patient factors determine whether you give a wait-and-see prescription?

What clinical factors determine whether you give a wait-and-see prescription?

What factors of the consultation/the circumstances determine whether you give a wait-and-see prescription?

Can you tell about a spesific consultation in which you gave a wait-and-see prescription?

Appendix C – GP questionnaire

UNIVERSITETET
I OSLO

VENT OG SE-
resept studien

Seksjon for allmennmedisin
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N-0318 Oslo

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Telefaks: +47 22 85 06 50
Mobil: +47 40 45 17 47
E-post: sigurd.hoye@medisin.uio.no

Legeskjema

ID-nr:.....

1. Hoveddiagnose: .....

2. Konsultasjonsdato: .....

3. Pasientens fødselsår: .....

4. Pasientens kjønn: ☐ Kvinne ☐ Mann

5. Hva var årsaken til at du valgte vent-og-se-resept til denne pasienten nå? (sett kun ett kryss ved det som passer best)

☐ Usikker diagnose
☐ Usikker på indikasjon for antibiotika
☐ Uenig med pasienten om behov for antibiotika
☐ Vanskelig å få til ønsket oppfølging de nærmeste dagene
☐ Andre årsaker:.....

6. Syntes du vent-og-se-resept var et fornuftig valg for denne pasienten?

☐ Svært fornuftig
☐ Ganske fornuftig
☐ Usikker

7. Tror du pasienten (eller pårørende, hvis pasienten er barn) hadde et ønske om en antibiotikaforskrivning ved denne konsultasjonen?

☐ Ja ☐ Nei ☐ Usikker

8. Tror du pasienten (eller pårørende, hvis pasienten er barn) er fornøyd med å ha fått en vent-og-se-resept?

☐ Ja ☐ Nei ☐ Usikker

9. Tror du pasienten vil hente ut denne resepten?

☐ Ja ☐ Nei ☐ Usikker

Husk å gi pasienten eget spørreskjema påført samme identitetsnummer!

University of Oslo

Appendix D – Patient questionnaire

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VENTOGSE-
resept studien

Pasientskjema

ID-nr: .....

Legen din gav deg nettopp en resept på antibiotika (medisin mot bakterieinfeksjon), men du fikk beskjed om å vente en periode før du bestemte deg for om du skulle ta medisinen eller ikke. Vi er svært interessert i å få vite hva du tenker rundt dette. Hvis antibiotikaen ble skrevet ut til ditt barn ber vi deg svare for ham/henne. Skjemaet skal fylles ut når du har begynt med antibiotikaen eller har bestemt deg for å ikke begynne med antibiotikaen.

Hvilke plager førte til at du gikk til legen? (sett kryss ved alle alternativ som passer)

☐ sår hals
☐ hoste
☐ øresmerter
☐ tett nese
☐ rennende nese
☐ ansiktssmerter/trykk over bihulene
☐ feber
☐ muskelsmerter
☐ sykdomsfølelse
☐ surklete/tett pust
☐ annet: .....

Hvor syk følte du deg da du gikk til legen?

☐ veldig syk ☐ ganske syk ☐ litt syk ☐ ganske frisk

Før du kom til legen, forventet du at han/hun ville… (sett kryss ved alle alternativ som passer):

☐ gi deg resept på antibiotika?
☐ gi deg resept på en annen type medisin?
☐ berolige deg eller gi deg råd?
☐ ta prøver?
☐ gi deg henvisning til spesialist?
☐ gi deg en sykmelding?
☐ jeg hadde ingen spesielle forventninger

Da legen foreslo at du selv skulle avgjøre om du skulle ta antibiotika, hvor sikker følte du deg på å kunne ta denne avgjørelsen selv? (sett kryss ved ett av alternativene)

☐ svært sikker
☐ ganske sikker
☐ verken sikker eller usikker
☐ ganske usikker
☐ svært usikker

Hvis du får et tilsvarende problem i fremtiden, ville du likt å få forskrevet antibiotika på samme måten da? (At du selv får avgjøre om du skal ta antibiotika eller ikke)

☐ Ja ☐ Nei ☐ Usikker

De to hovedtypene av mikroorganismer som kan gi infeksjon er virus og bakterier. Føler du at du har kunnskap om forskjellen mellom disse to typene?

☐ ingen kunnskap ☐ noe kunnskap ☐ god kunnskap ☐ svært god kunnskap

SNU ARKET

UNIVERSITETET I OSLO
Seksjon for allmennmedisin

Vi vil gjerne vite om du tok noe av antibiotikaen du fikk forskrevet. Prøv å svare så ærlig som mulig – vi er ikke interessert i "riktig" eller "feil" svar, vi vil kun vite hva som skjer når antibiotika blir forskrevet på denne måten.

Begynte du å ta antibiotikaen?

☐ Ja
Fortsett på spørsmålene i denne kolonnen

Når begynte du å ta antibiotikaen? (Sett kun ett kryss)
☐ Samme dag jeg var hos legen
☐ Dagen etter jeg var hos legen
☐ Dagen etter det igjen
☐ 3 til 7 dager etter at jeg var hos legen
☐ Mer enn en uke etter at jeg var hos legen.

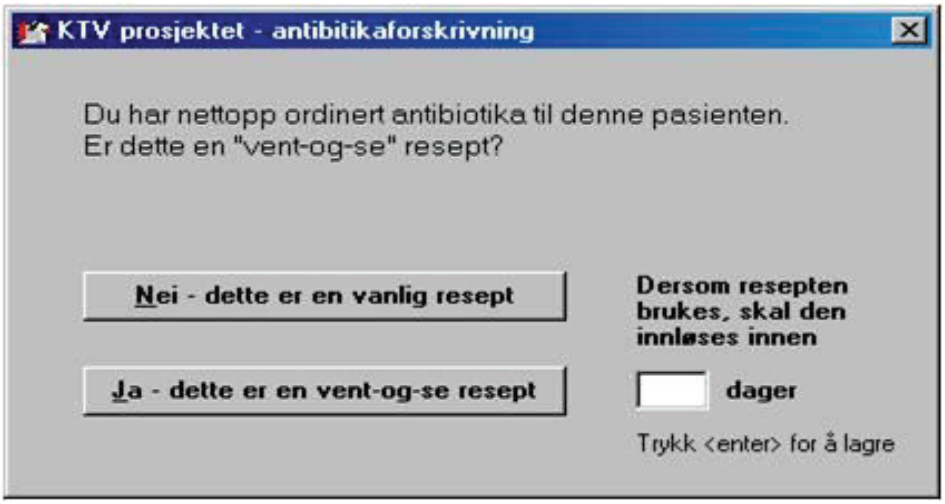
Hvorfor bestemte du deg for å starte med antibiotikaen? (Sett kryss ved alt som passer)
☐ For å være på den sikre siden
☐ Jeg mente jeg burde ha antibiotika i utgangspunktet
☐ Plagene varte for lenge (Hvor lenge?.....)
☐ Plagene ble verre
☐ Jeg var bekymret for enkelte av plagene (Hvilken plage/hvilke plager?.....)
☐ Usikker på hva jeg skulle gjøre, så jeg bare tok den
☐ Andre årsaker: .....

☐ Nei
Fortsett på spørsmålene i denne kolonnen

Hvorfor bestemte du deg for ikke å starte med antibiotikaen? (Sett kryss ved alt som passer)
☐ Jeg mente det var unødvendig i utgangspunktet
☐ Plagene ble bedre eller helt borte
☐ Jeg var redd antibiotikaen ikke kunne taes sammen med annen medisin jeg bruker
☐ Jeg var redd for bivirkninger
☐ Usikker på hva jeg skulle gjøre, så jeg bare lot være å ta den
☐ Andre årsaker: .....

Hva har du gjort med resepten?
☐ Kastet den
☐ Spart den til senere
☐ Hentet ut antibiotikaen fra apoteket, men kastet den eller leverte den tilbake
☐ Hentet ut antibiotikaen fra apoteket og spart den til senere

Hva er din høyeste gjennomførte utdannelse? (Her skal du svare for deg selv og ikke for ditt barn)
☐ grunnskole
☐ videregående skole
☐ høyskole/universitet

Takk for hjelpen! Vær vennlig å returnere dette skjemaet i vedlagte ferdigfrankerte konvolutt.

Appendix E – Pop-up window