Urinary tract infections in primary care. Antimicrobial resistance, treatment and outcome.

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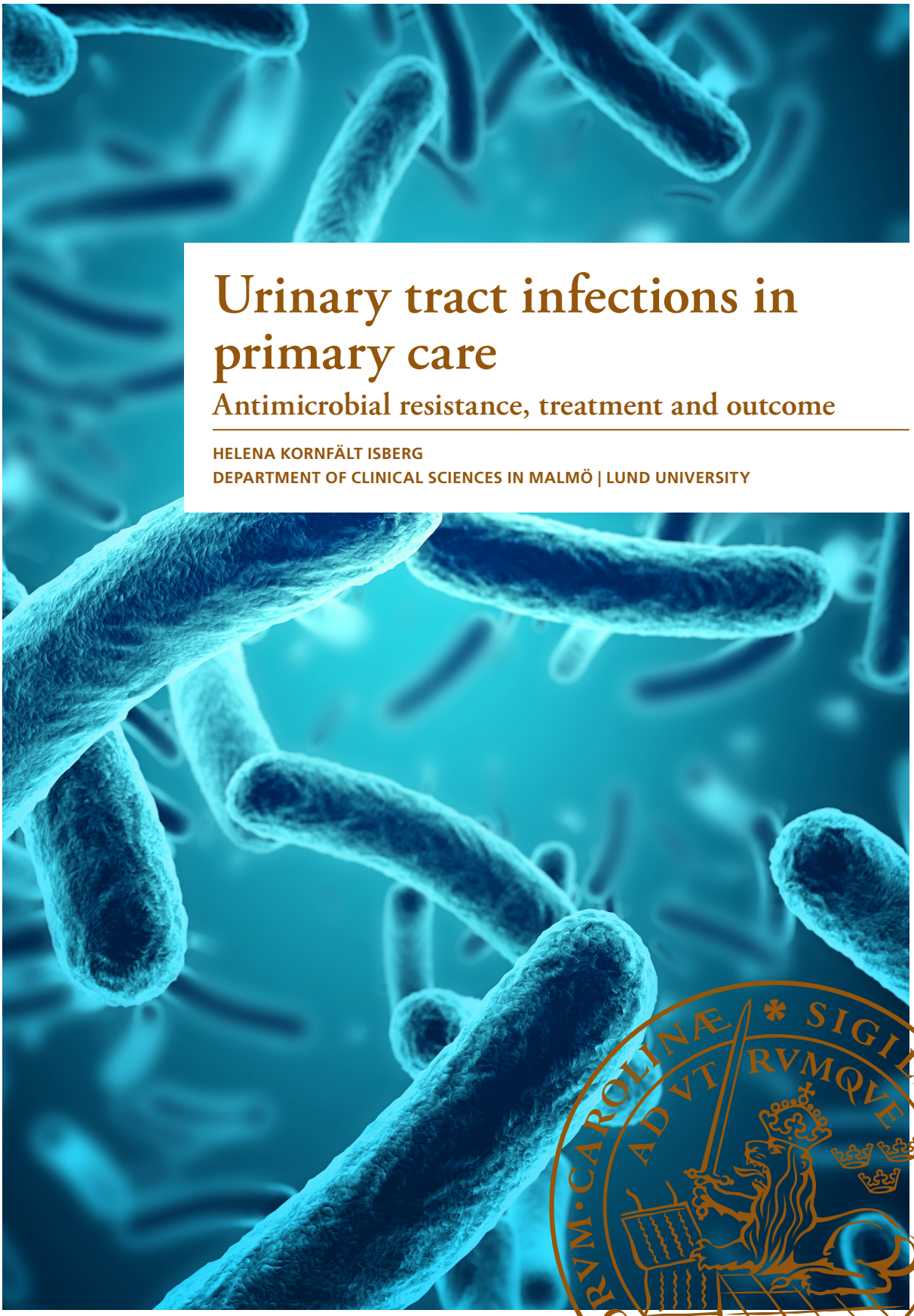

Urinary tract infections in primary care

Antimicrobial resistance, treatment and outcome

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Antimicrobial resistance, treatment and outcome

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Urinary tract infections in primary care. Antimicrobial resistance, treatment and outcome

Introduction: Antibiotic resistance is a growing public health problem and high antibiotic pressure is one of the key drivers of this issue. The majority of all antibiotic prescribing in Sweden is done in outpatient care, and urinary tract infections (UTIs) are the second most common cause of prescribing after upper respiratory tract infections. UTIs are much more common in women than in men and most studies on UTIs are performed in women. This thesis includes data on both women and men with UTIs.

Aims: To describe urinary tract infections in primary health care with regards to clinical symptoms, treatment outcome, antibiotic resistance and adherence to treatment guidelines.

Methods: In Paper I, data from the Primary Care Record of Infections in Sweden (PRIS) were analysed with regards to UTIs, stratified by age and sex. Changes in antibiotic prescribing between the years 2008, 2010 and 2013 as well as adherence to treatment guidelines were followed. The data in Paper II and III comes from a prospective study on uncomplicated UTIs performed at eight different primary health care centers in southern Sweden between 2014 and 2016. Women aged 17 years and older attending with symptoms indicating uncomplicated UTI were included. Patients answered anamnestic questions about former infections, antibiotic treatment and symptoms in a questionnaire. They were also asked to fill out a symptom diary describing symptoms after the clinical visit. Urine samples were analysed, and susceptibility testing was conducted. Data in Paper IV were based on information from electronic medical records. Data on diagnosis of lower UTIs and antibiotic prescribing for men 18-79 years in five different Swedish counties between 2012 and 2015 were analysed with focus on antibiotic choice and therapy failure, recurrence and complications.

Results: Data from the PRIS record shows a major change in prescribing of antibiotics commonly used in the treatment of lower UTIs among patients in primary health care. Prescription rates of narrow-spectrum antibiotics increased in-line with treatment guidelines. Swedish general practitioners followed clinical recommendations in the treatment of lower UTIs in women. Prescription rates of broad-spectrum antibiotics to men were still high in 2013 (Paper I). Antibiotic resistance in *E.coli*, was rare and was associated with antibiotic treatment within the last year. The empirically prescribed antibiotics were in-line with treatment recommendations (Paper II). The women had symptoms for several days before attending the primary health care centre and symptoms often lasted for several days after the visit. A majority of patients felt restricted in their daily activities. Older women and women not treated with antibiotics had the longest symptom duration (Paper III). In Paper IV no difference in complication rates between men who received narrow- and broad-spectrum antibiotic treatment was found. Patients prescribed narrow-spectrum antibiotics and trimethoprim had higher odds of having a reconsultation because of therapy failure and recurrence.

Conclusions: A majority of patients with symptoms indicating UTI were treated with antibiotics and treatment was in-line with Swedish treatment recommendations. Antibiotic resistance in E.coli among women with UTI was low. In women, older age and not being treated with antibiotics were factors associated with longer symptom duration after consultation. No difference in outcome regarding complications was identified between men diagnosed with lower UTI treated with narrow or broad spectrum antibiotics. Reconsultations due to therapy failure and recurrence was more common in men treated with narrow-spectrum antibiotics and trimethoprim as compared to ciprofloxacin and trimethoprim/sulfamethoxazole.

Keywords: urinary tract infection, antibiotic prescribing, antimicrobial resistance, primary health care, guideline, adherence, Escherichia coli

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Abstract

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treatment recommendations (**Paper II**). The women had symptoms for several days before attending the primary health care centre and symptoms often lasted for several days after the visit. A majority of patients felt restricted in their daily activities. Older women and women not treated with antibiotics had the longest symptom duration **(Paper III).** In **Paper IV** no difference in complication rates between men who received narrow- and broad-spectrum antibiotic treatment was found. Patients prescribed narrow-spectrum antibiotics and trimethoprim had higher odds of having a reconsultation because of therapy failure and recurrence.

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A majority of patients with symptoms indicating UTI were treated with antibiotics and treatment was in-line with Swedish treatment recommendations. Antibiotic resistance in *E.coli* among women with UTI was low. In women, older age and not being treated with antibiotics were factors associated with longer symptom duration after consultation. No difference in outcome regarding complications was identified between men diagnosed with lower UTI treated with narrow or broad spectrum antibiotics. Reconsultations due to therapy failure and recurrence was more common in men treated with narrow-spectrum antibiotics and trimethoprim as compared to ciprofloxacin and trimethoprim/sulfamethoxazole.

Abbreviations

ABU	Asymptomatic bacteriuria
AMR	Antimicrobial resistance
BIT	Bladder incubation time
BSI	Bloodstream infection
CFU	Colony forming units
DDD	Defined daily doses
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ESBL	Extended spectrum beta lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Collaboration to Standardise Surveillance of Antimicrobial Resistance
GP	General practitioner
LUTS	Lower urinary tract symptoms
NPV	Negative predictive value
OTC	Over the counter
PHC	Primary health care
PHCC	Primary health care centre
POCT	Point-of-care test
PPV	Positive predictive value
PRIS	Primary Care Record of Infections in Sweden
RCT	Randomised controlled trial
STI	Sexually transmitted infection
Strama	Swedish Strategic programme against antibiotic resistance
UTI	Urinary tract infection
WHO	World Health Organization

Definitions

Urinary tract infection (UTI): An infection in any part of the urinary tract.

Asymptomatic bacteriuria: Significant growth of bacteria in urine but with no clinical UTI symptoms.

Lower UTI: (Cystitis) A bladder infection engaging the lower urinary tract

Uncomplicated UTI: A lower UTI in a non-pregnant woman with no factor such as structural and neurological abnormalities that will render her more susceptible to develop a UTI.

Complicated UTI: A UTI in a woman or man with structural or functional abnormalities of the urinary tract.

Recurrent UTI: Two or more UTIs in the last six months or three or more UTIs in the last 12 months.

Febrile UTI (pyelonephritis/acute prostatitis): A bacterial infection with tissue inflammation of the urinary tract, most often affecting the upper urinary tract and kidneys (pyelonephritis) or prostate (acute prostatitis) and results in a systemic inflammation.

Sepsis: A condition with life-threatening organ dysfunction caused by a dysregulated host response.

Original papers

This thesis is based on the following papers referred to in the text by their Roman numerals.

I. Kornfält Isberg H, Hedin K, Melander E, Mölstad S, Beckman A: Increased adherence to treatment guidelines in patients with urinary tract infection in primary care: A retrospective study. *PlosOne.* 2019, 14:3

II. Kornfält Isberg H, Melander E, Hedin K, Mölstad S, Beckman A: Uncomplicated urinary tract infections in Swedish primary care; etiology, resistance and treatment. *BMC Infectious Diseases.* 2019, 19:155

III. Kornfält Isberg H, Hedin K, Melander E, Mölstad S, Beckman A. Uncomplicated urinary tract infection in primary health care; presentation and clinical outcome. *Infectious Diseases*. Published online 19 Oct 2020.

IV. Kornfält Isberg H, Hedin K, Melander E, Mölstad S, Cronberg O, Engström S, Lindbäck H, Neumark T, Stridh-Ekman G, Beckman A. Different antibiotic regimes in men diagnosed with lower urinary tract infection-a register-based retrospective study. *Scandinavian Journal of Primary Health Care*. 2020, 20:1

Introduction

According to the World Health Organization (WHO), antibiotic resistance is one of the largest threats to global health and misuse of antibiotics is accelerating the progress [1, 2]. The most common bacteria causing urinary tract infection (UTI) is Escherichia coli (*E.coli*) and this is also one of the most commonly reported resistant bacteria worldwide. Lower UTIs are common in primary care and lead to a high number of antibiotic prescriptions. The aim of antibiotic treatment in patients with lower UTIs is to relieve and to shorten the duration of symptoms. A high number of antibiotic prescriptions can, lead to high antibiotic pressure, which enhances the development of antibiotic resistance. Prudent antibiotic prescribing is important to preserve the effectiveness of antibiotics. National treatment guidelines for antibiotic prescribing in UTI help prescribers in decisions regarding prescribing. It is important to evaluate the adherence to guidelines, antibiotic prescribing and antibiotic resistance of infections frequently managed in primary care, and we also need to follow the clinical outcome in patients with UTIs treated in primary health care. When the antibiotic resistance situation is monitored and treatment guidelines are developed in order to direct the antibiotic treatment to infections that really need treatment, we also have to follow the clinical cure in patients not to cause any harm when restricting treatment.

This thesis focuses on antimicrobial resistance, antibiotic treatment, adherence to treatment guidelines and treatment outcome among patients with lower UTI in primary care.

Background

Antibiotic consumption

The discovery of penicillin by Alexander Fleming in 1928 was an important cause of improved public health during the 20th century and modern health care depends on antibiotics [1]. For more than 50 years we have been using antibiotics to treat infections but also in other areas such as giving antibiotics to animals in food production to promote growth and to treat infections in plants [3]. This over-use of antibiotics has accelerated the process of increasing antibiotic resistance. Today bacteria have developed resistance mechanisms to all known antibiotics [3]. Antimicrobial-resistant organisms are found in people, food, animals, plants and the environment, and they can move between ecosystems [4]. Pathogens do not respect national borders and are thus spread worldwide [5].

Antibiotic consumption worldwide, in Europe and in Sweden

Over-prescribing of antibiotics is a leading cause of increasing prevalence of antibiotic resistance. The WHO considers increasing prevalence of antibiotic resistance as a threat against global health and, without urgent action, we are heading towards a post-antibiotic era, in which common infections and minor injuries can once again kill [1]. In countries where antibiotics can be purchased without prescription, the emergence and spread of resistance is made worse [1]. The WHO is monitoring data of antimicrobial consumption worldwide. The use of antibiotics is very high in some parts of the world, which suggests over-use, but low in some countries, which could indicate low access to medication but could also be due to better antibiotic prescribing. Worldwide, a suspected UTI is the second most common reason for prescribing of antibiotics in outpatient care and the most common reason for antibiotic prescribing to the oldest patients [6, 7].

There is a wide intra- and interregional variation in the total amount of antibiotics prescribed and the choice of antibiotics used [4].

The European Centre for Disease Prevention and control (ECDC) documents on European antibiotic consumption in annual reports [8]. Antimicrobial consumption is expressed as the number of defined daily doses (DDD) per 1000 inhabitants per day. In 2017 the average consumption of antibacterials for systematic use in Europe was 23.4 DDD per 1000 inhabitants with a wide range of 11.0-34.1 DDD per 1000

inhabitants. In 2017, consumption of antibacterials for systematic use in the community within Europe varied between countries (Figure 1). More antibiotics were prescribed in southern countries compared to northern countries [8].

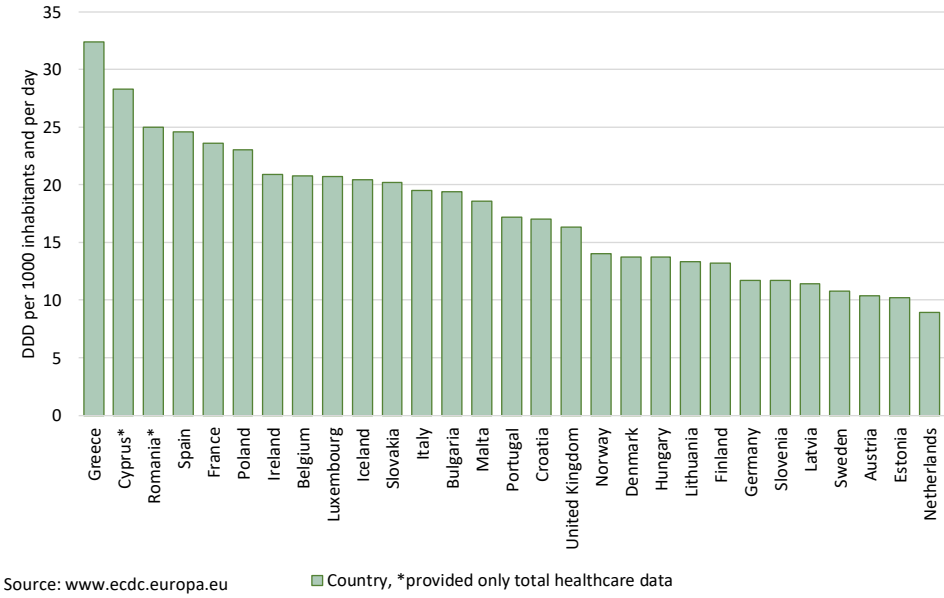


Figure 1. Consumption of Antibacterials for systemic use (ATC group J01) in the community (primary care sector) in Europe, reporting year 2018. (data source www.ecdc.europa.eu)

Variations in prescribing are also seen within Sweden with differences in the prescribing pattern between different regions, different health care centres and different prescribers [9, 10]. These differences could be explained by differences in health status among the population, cultural aspects of prescribing, habits of prescribing, and education among prescribers and could imply that there is a potential of further decreasing antibiotic prescribing without a risk of increased morbidity [9, 10]. Many actions have been taken in Sweden to work towards more prudent antibiotic prescribing. Collaborations between different authorities such as the Public Health Agency of Sweden, the National Veterinary institute and the Swedish Medical Products Agency has led to a favourable decline in antibiotic use. Antibiotic use for growth promotion in animal husbandry was banned in 1986 and since then the total sales of antibiotics have decreased by around two thirds. In 2018 a total of 60 tonnes of antibiotics were sold for human use and 10 tonnes for animal use [10].

The Swedish strategic programme against antibiotic resistance (Strama) was created in 1995. Strama has since then been working on a local and national level with

monitoring of antibiotic use for informed decision making, national targets for antibiotic prescribing, surveillance of antibiotic resistance and communication to raise awareness for action and behavioural change [11]. Important factors for change to better antibiotic prescribing have been to set a national target for the number of prescriptions in outpatient care, defining quality indicators based on treatment recommendations and providing local feedback to prescribers [11].

Antimicrobial resistance

Surveillance of antimicrobial resistance

To improve the evidence base of antimicrobial resistance (AMR), the WHO launched a global collaboration to standardise surveillance of AMR (GLASS) in 2015. The report from GLASS provides data on resistance for pathogens from over 40 countries and results show that the most commonly reported resistant bacteria are *Escherichia coli (E.coli), Klebsiella pneumoniae, Staphylococcus aureus* and *Streptococcus pneumoniae*, followed by *Salmonella* spp. There is a wide variation in rates of AMR in different countries [5] and the data also reports high rates of resistance to antibiotics commonly used to treat serious bacterial infections in many countries across the world [4].

The ECDC has created a surveillance network called (the European Antimicrobial Resistance Surveillance Network (EARS-Net)) that reports AMR data from Europe [12]. The data shows that AMR is a serious challenge with high rates of resistance for several bacterial species and antimicrobial group combinations. In general, lower resistance rates are reported from countries in the north, and higher rates are reported from countries in the south and east of Europe [12]. The map in Figure 2 illustrates the differences in antibiotic resistance to fluoroquinolones in invasive *E.coli* in Europe.

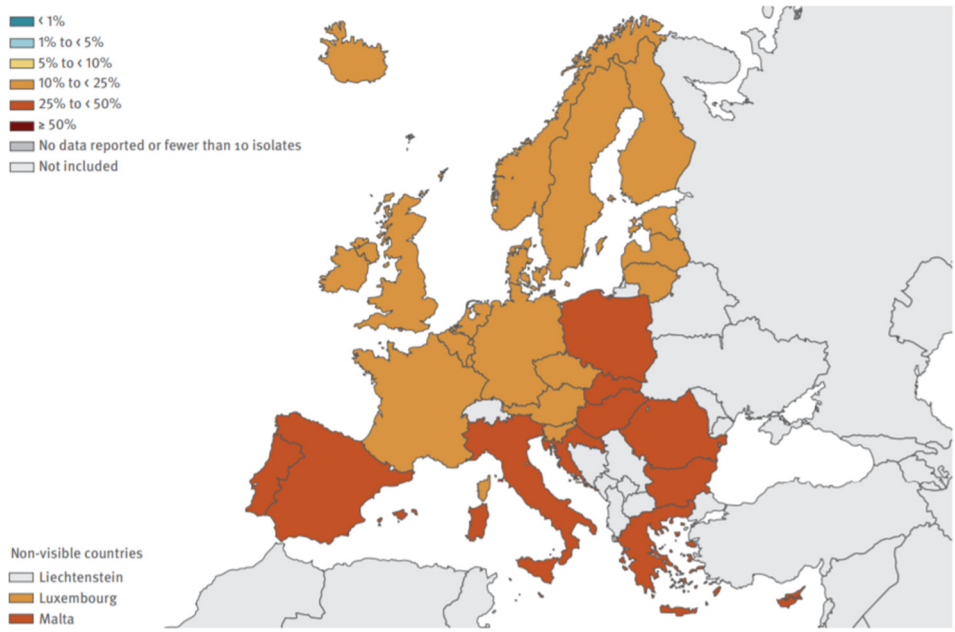


Figure 2. Escherichia coli. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2018. (source: www.ecdc.europa.eu)

In Sweden, data on resistance in bacteria from humans are obtained from the clinical microbiological laboratories via Svebar and are compiled by the Public Health Agency of Sweden in Swedres [10]. Svebar is an automated system, which collects AMR data from clinical isolates from humans from the local clinical microbiology laboratories. At present 20 laboratories deliver data to Svebar (March 2020) [13].

The antibiotic resistance situation in humans and animals in Sweden is still favourable compared to many other countries in the world. Levels of antibiotic use and antibiotic resistance are among the lowest in the European Union (EU) [2, 8, 11].

Mechanisms for antibiotic resistance

The most common pathogen causing UTI is *E.coli*, which belongs to the family Enterobacteriales. In Enterobacteriales, the clinically most important mechanisms causing antibiotic resistance are spontaneous mutations, that for example, cause resistance against quinolones, mecillinam and nitrofurantoin. Uptake of resistance genes from other bacteria is called horizontal gene transfer, the resistance genes are transferred via plasmids (genetic movable elements). Plasmids often contain many resistance genes and sometimes also virulence genes. A bacterium can, by uptake of a plasmid, become multi resistant very fast [7, 14]. Extended spectrum beta lactamase (ESBL), trimethoprim and sulfa resistance are spread by plasmids [15].

All antibiotic use promotes the development and spread of resistance genes but also the spread and colonialization of already resistant strains [16, 17]. The high prevalence of UTI and the frequent antibiotic use to treat UTIs favours this development [15, 18]. In an environment with high antibiotic pressure with only a few possible antibiotic choices, like in the treatment of UTIs, this becomes a problem [15].

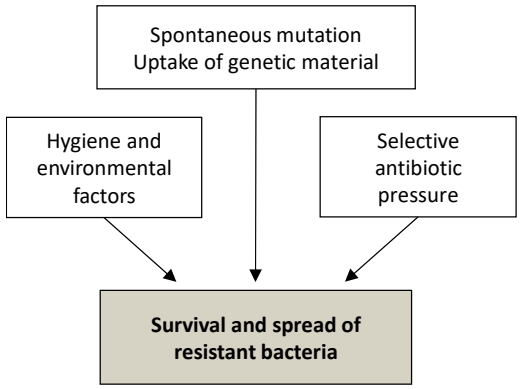


Figure 3. Factors affecting the developement and spread of resistant bacteria. (source: Lakemedelsboken.se)

Resistance and urinary tract infections

E.coli

E.coli is part of the common human gut flora but is also the most common cause behind bloodstream infections and UTIs in Europe. *E.coli* accounts for 75-90% of all reported cases of UTI [19, 20].

E.coli is one of the most commonly reported resistant bacteria worldwide but there are great variations in rates between countries [2, 8]. Infections caused by antimicrobial-resistant *E.coli* proportionally contribute the most to the burden of AMR in the EU/EEA, both as number of cases and number of attributable deaths [8]. For *E.coli,* combined resistance to several antimicrobial groups are common and the production of ESBL is one mechanism of resistance of special concern affecting *E.coli*. Bacteria producing ESBL (most commonly *E.coli* but also *Klebsiella* spp.) can break down penicillins and cephalosporins and are thus resistant to those antibiotic agents [3]. 50% of bacteria producing ESBL are also resistant to aminoglycosides, quinolones and trimethoprim/sulfamethoxazole and can only be treated with intravenous carbapenems meaning that patients with uncomplicated UTIs may have to be hospitalised and treated with antibiotics due to antibiotic resistance, thus creating high costs for society. Enterobacteriales with $ESBL_{CARBA}$ are extremely resistant as they, in addition to above mentioned resistance in ESBL-producing bacteria are also resistant to carbapenems and so there are few treatment

options in case of infection. The number of $ESBL_{CARBA}$ producing bacteria is still rare in Sweden [10]. There is a diversity in prevalence of ESBL- producing bacteria between countries; the prevalence is high in several Asian countries and still low but increasing in Sweden. The number of bloodstream infections (BSI) with ESBL-producing Enterobacteriales has increased steadily since mandatory reporting of ESBL isolates started in Sweden in 2007. In 2019 *E.coli* was the most common cause of BSI (82%) and 7.6% of *E.coli* isolates causing BSI were ESBL-producing. In 2019 the incidence of ESBL- producing Enterobacteriales was 104 new cases per 100 000 inhabitants [13]. There is an association between high antibiotic prescribing and the occurrence of ESBL- producing bacteria [3, 8].

National data on antibiotic resistance in Sweden (including both hospital- and primary care) show that the resistance to fluoroquinolones in *E.coli* is now at approximately 11% for urine and 14% for blood isolates [10, 13]. Increasing rates of resistance in *E.coli* to trimethoprim has been reported in the last 15 years and is now about 20%, even higher if recently treated with trimethoprim [10]. In 2019 resistance rates in *E.coli* isolates found in urine samples was 4.8% for mecillinam and 1.2% for nitrofurantoin [13].

Within Sweden, antibiotic resistance rates for *E.coli* differ between sex and age and between hospital and primary health care [13, 21, 22]. It is therefore important to follow resistance rates for targeted populations such as patients in primary health care. When reporting resistance numbers laboratories normally do not separate primary care cultures from hospital care cultures, which makes it difficult to get a representative overview of the resistance situation in primary care. Microbiological data on aetiology and bacterial susceptibility presented from laboratories probably represent a selected and thus potentially biased sample of patients with complicating factors. Patients in hospital care with complicated infections are often treated with broader-spectrum antibiotics which could result in higher prevalence of antibiotic resistant bacteria in this group of patients as compared to patients seeking care in primary health care. We need better knowledge about the antibiotic resistance situation in primary care in order to choose the correct empirical antibiotic treatment for patients in primary care.

Urinary tract infection

Epidemiology

UTI is a common cause of visits and antibiotic prescribing in primary care. The incidence of UTIs varies between age-groups and sex. In the Netherlands UTIs were the most common reason to consult a general practitioner (GP) with 323 contacts per 1000 women in 2014, in men the corresponding number was 37 contacts per 1000 men [23]. Information on incidence of UTIs is often based on information on

prescriptions from primary care. UTI is often a self-limiting condition and the real incidence in the younger population is probably higher than reported by incidence numbers. Among older people, asymptomatic bacteriuria (ABU) is common in both women and men and UTI is often over-diagnosed. In children younger than 6 months UTI is more common in boys than in girls. For all other ages, UTI is more common in women [7]. Nearly 50% of all women will experience a UTI during their lifetime and each year 10-13% of all women will have a UTI. The infection is most common in women aged 18-34 years, the incidence declines thereafter and increases again among the elderly [24]. Recurrent UTI is common (meaning 2 or more UTIs within 6 months or 3 or more within one year). Among women with lower UTI, 25-30% will experience a new UTI within 6-12 months [7].

UTI in men is less common than in women and is uncommon in younger men [25]. The incidence increases with age and is around 0.9-2.4 cases per 1000 men in those younger than 55 years, and 7.7 cases per 1000 men among those 85 years and older. Among the oldest, incidence rates are about equal for men and women [26-28]. The anatomical differences between women and men with a much shorter urethra in women, a shorter distance from the urethral opening to the bladder and a shorter distance from the urethral meatus to the anus (where potential uropathogens live) in women as compared to men can explain some of the differences in incidence of UTIs between younger women and men [29].

Pyelonephritis is much less common than lower UTI. The annual incidence in women is 0.39-2.4% and in men 0.08- 0.24% [7]

Bacteria causing UTI

In women younger than 50 years, 80% of all UTIs are caused by *E.coli*. The second most common bacteria in this group of patients *is Staphylococcus saprophyticus* (*S. saprophyticus*), followed by the gram negative *Klebsiella* spp.*, Pseudomonas aeruginosa* and *Proteus* spp. and gram-positive enterococci and aerococci [7, 29]. Non-*E.coli* UTI is more common in men, in individuals with recurrent UTIs and patients with urinary catheter or obstruction [29].

Pathogenesis in women

E.coli is part of the normal bacterial gut flora and is the most common bacteria causing UTI in healthy women [19]. The bacteria colonise the rectal and periurethral area and can also be part of a distal urethral and vaginal colonisation [30]. Changes in the vaginal environment (normal flora) caused by recent antimicrobial therapy [31] or spermicide use [32] may facilitate colonisation by uropathogenic *E.coli.* The bacteria enter the bladder via the urethra and can also affect the ureters and kidneys. *E.coli* strains which cause UTI, have several virulence factors that increase their ability to colonise and persist in the urogenital tract [33]. The adhesion to the urothelial surface via bacterial P fimbriae and type 1-fimbriae, prevents the washout via micturition and allows the bacteria to persist in the bladder. Most UTIs cannot

be explained by functional or anatomic abnormalities in the urinary tract but there are several risk factors for UTI where being a woman is one of the major risk factors. Other important risk factors are prior UTI, sexual activity, placement of urinary catheter, genetic susceptibility and anatomic abnormalities [29].

Pathogenesis in men

Infections of the urinary tract and in the male genitalia can be difficult to separate from each other as they can cause similar symptoms.

When men get older, structural and functional changes impair normal voiding thus making it harder for the urine to pass through the urine-tract. Benign prostatic hyperplasia can lead to obstruction and a turbulent flow of urine that can cause UTI [25].

Chronic bacterial prostatitis is a disease that causes pain in the lower abdomen, perineum, scrotum or testis. Chronic bacterial prostatitis can also appear without symptoms or with recurrent, symptomatic UTI with or without fever [7]. The condition can sometimes be hard to differ from lower UTI in men. The frequency of lower UTI or ABU associated with infection in the prostatic gland is unknown. Chronic bacterial prostatitis is sometimes discussed in terms of a confounder in studies with the aim to describe the incidence and outcome in lower UTI in men. Bacteria causing UTI and chronic benign prostatitis in men are more prone to form biofilm than bacteria causing UTI in women. The ability to form biofilms is a survival strategy for the bacteria and prevents the access of antimicrobial agents [34, 35].

Clinical presentation

Classical symptoms of lower UTI are increased frequency of micturition, urgency and dysuria, in some cases suprapubic pressure and malaise [29]. Patients with lower UTI can experience troublesome symptoms although the condition, in most cases, is harmless and often self-limiting. Pyelonephritis due to untreated lower UTI is a common cause of concern among both prescribers and patients but is in fact uncommon (0.5-2.6%) [20, 36, 37]. Research based on patients' experiences from lower UTI describes a wide range of symptoms such as stomach ache, feeling hot, feeling out of sorts [38, 39], usually not mentioned as classical symptoms in clinical studies and often lasting more than three days [40]. In a study on women treated with antibiotics due to lower UTI, a higher symptom severity score at first visit was correlated with longer duration of the complaints, moreover, a positive urine culture analysis result predicted a shorter duration of symptoms [40]. In a British primary health care study, patients with a history of lower UTI, frequent somatic symptoms and severe symptoms at baseline were likely to have severe symptoms lasting longer than three days. More severe symptoms were described by patients that were not prescribed antibiotics, or by patients with growth of bacteria resistant to antibiotics [41].

Different studies from Europe and America show that women with lower UTI need to take sick-leave for 1-3 days, are limited in their activities for 2-4 days and recurrence of their infection is related to mental stress [42, 43].

Although UTI is regarded as a benign infection, the symptoms have a negative impact on women's daily life, and a negative effect on the quality of life for women suffering from UTI [44, 45]. A negative effect on quality of life caused by side effects of antibiotic treatment has also been reported [44].

High societal costs related to lower UTIs in women have been reported in studies from different countries [46, 47].

Lower UTI-the diagnose

In both women and men, the clinical diagnosis of lower UTI is based on the medical history. Classic lower urinary tract symptoms include dysuria, frequent voiding of small volumes, urinary urgency and absence of fever or raise in infection parameters such as CRP [7]. Symptoms indicating lower UTI are indications for empirical treatment in general practice. The term empirical antibiotic treatment indicates that it is based on experience and is directed against an anticipated cause of infection, taking into account the risk for presence of drug resistant strains. According to Swedish treatment guidelines, no further diagnostic examination is needed in women if no complicating factors are present. Since AMR is more common in men than in women, a urine culture should always be performed prior to antibiotic treatment in men [7, 48-50].

A urine culture with growth of bacteria in combination with clinical symptoms is the gold standard for the diagnosis of a lower UTI [7, 48]. To decide whether bacterial growth in a urine sample is significant both the bacterial species and the bacterial concentration must be considered. The detection of 10^3 colony forming units (CFU)/ml for *E.coli* and *S saprophyticus* is considered to be significant for both men and women.

For less pathogenic bacteria (secondary pathogens) as *other Enterobacteriales, Enterococcus and S. agalactiae,* higher concentrations of bacterial growth ($\geq 10^4$ CFU/ml) are considered to be significant in women. For doubtful uropathogens even higher concentrations are needed to be considered as significant in women ($\geq 10^5$ CFU/ml). In men, growth of bacteria is considered significant if the number of CFU/ml is $\geq 10^3$ independent of pathogen [7, 48].

The duration of bladder incubation before the urine sample is collected affects the concentration of bacterial growth in the urine sample. The optimal incubation time is ≥4 hours [51, 52] but this is often hard to achieve due to symptoms such as urgency and frequent micturition.

Urine dipsticks are frequently used in the diagnostic testing as they are easy to handle, and they can be read directly [48]. The dipsticks are used to detect urine

samples with bacterial growth. As a help in the diagnostic process the GP often takes the answer from the nitrite and leukocyte test into consideration. Nitrite is a metabolic product of nitrate-reducing bacteria, for example *E.coli*. The bladder incubation time (BIT) should be ≥4 hours for a reliable test. In a patient with a UTI, the test has a relatively low sensitivity of 53-65%, the specificity is 81-96% [53]. The leukocyte test detects white blood cells that in high numbers can indicate a UTI but can also indicate other inflammations such as vaginitis. The leukocyte test has a sensitivity of 71-100% and a specificity of 4-62% [53, 54]. Accordingly, the diagnostic precision of urine dipstick test is low and studies have been performed to analyse the accuracy in diagnostic testing with urine dipsticks. The negative predictive value (NPV) is low, especially when the probability for a UTI is high. [55-57].

Asymptomatic bacteriuria

A patient with ABU has no symptoms of UTI but there are bacteria in the urine. Kass defined ABU in 1956 as the growth of $\geq 10^5$ CFU/ml of bacteria in urine in two consecutive cultures in a woman with no symptoms from the urinary tract [58]. Screening and treatment of ABU in women should in most cases be avoided but shall in some circumstances, such as pregnancy and prior to urinary surgery, be performed [48].The prevalence of ABU in otherwise healthy, non-pregnant young women varies from 2% to 5% [59]. The prevalence increases with age and is 3-9% in women aged 50 years and around 20% for women aged 80 years and over [59, 60]. For elderly women living in institutions, the prevalence is 25-50% [59, 61].

The definition of asymptomatic bacteriuria (ABU) in men is growth of $\geq 10^5$ CFU /ml in urine culture from only one voided sample in a man without UTI symptoms [62]. ABU is uncommon in younger men, the prevalence increases with age. In 80 year old residents living in the community, the prevalence is 10% [63] while prevalence is higher in institutionalised older men (15-40%) [61, 64]. All patients with a urine catheter have ABU after 2-3 weeks [7].

Differential diagnosis

Urethritis and vulvovaginitis

In urethritis, local symptoms such as frequent voiding and painful micturition dominate. These symptoms also appear in patients with lower UTI and the conditions are probably often confounded. Lower UTI is more likely when symptoms include frequency, urgency or haematuria, when symptom start is sudden or severe and when vaginal irritation or discharge is not present [65]. Urethritis can be caused by STI (sexually transmitted infections). In post-menopausal women, the most common cause is local oestrogen deficiency. Vulvovaginitis can give local symptoms secondary to inflammation caused by STI, candida infection and in older women vulvovaginal atrophy [66].

Pyelonephritis

Acute pyelonephritis is a bacterial infection engaging the upper urine tract and kidneys and causes a systematic inflammation. Common symptoms are fever, malaise, chills, back pain and flank pain. Up to one third of the patients do not demonstrate symptoms from the lower urinary tract. In 12-13% of patients with pyelonephritis, blood culture is positive, and the prevalence of positive blood cultures increases with age [7, 29].

Acute bacterial prostatitis

Acute bacterial prostatitis can be caused by ascending urethral infection or intraprostatic reflux and has increased as a result of diagnostic trans-rectal prostate biopsy. Common symptoms are acute onset of high fever, chills, suprapubic, rectal or perineal pain, tense prostate gland, urinary tract symptoms such as dysuria, frequency and urinary retention. The medical history and physical examination including urine and blood culture will support the diagnosis. Systemic symptoms are common. Prostatic abscess formation represents a severe complication of acute bacterial prostatitis [54, 67, 68].

Treatment guidelines for urinary tract infection

National treatment and prescribing recommendations for infectious diseases, including documentation of the assessment of supporting evidence, are published by the Swedish Medical Products Agency in collaboration with Strama. The aim with the guidelines is a better and safer use of antibiotics [7]. Since 2007 (women) and 2014 (men) the use of fluoroquinolones is no longer recommended in Sweden when treating lower UTI [15, 54, 69]. New national treatment guidelines for UTIs in primary care were published in 2017 [7].

In women, aged 15 years and older, the symptoms indicating a lower UTI described by the patient should decide whether to treat with antibiotics or not. Two or more of the symptoms dysuria, frequency and urgency should be present and if only mild or moderate symptoms, symptomatic treatment and increased water intake is recommended. For moderate symptoms, a delayed prescription can be done. If the patient experiences bad symptoms, antibiotics according to guidelines should be prescribed [7].

The guidelines recommend pivmecillinam and nitrofurantoin over trimethoprim against uncomplicated UTIs in women aged 15 years or older. Prescribers are also encouraged to minimise the use of fluoroquinolones due to increasing resistance rates among gram negative pathogens and due to high prevalence of side-effects related to the use of fluoroquinolones [7, 70]. Treatment with pivmecillinam and nitrofurantoin is also recommended in lower UTI in men but a urine culture should

always be performed in men prior to treatment, and men are recommended longer treatment duration than women [7].

Table 1a. Antibiotic choice, empiric treatment of urinary tract infection in non- pregnant women

Drug	Dosage	Course length (days)
First choice		
Pivmecillinam	200 mg x 3 400 mg x 2	5 3*
Nitrofurantoin **(no effect if GFR<40 ml/min)**	50 mg x 3	5
Second choice		
Trimethoprim	160 mg x 2	3
Cefadroxil	0.5 g x 2 or 1 g x 1	5

*Treatment duration for 5 days (200 mg x 3) may be needed in postmenopausal women

Table 1b. Antibiotic choice, empiric treatment of urinary tract infection in men*

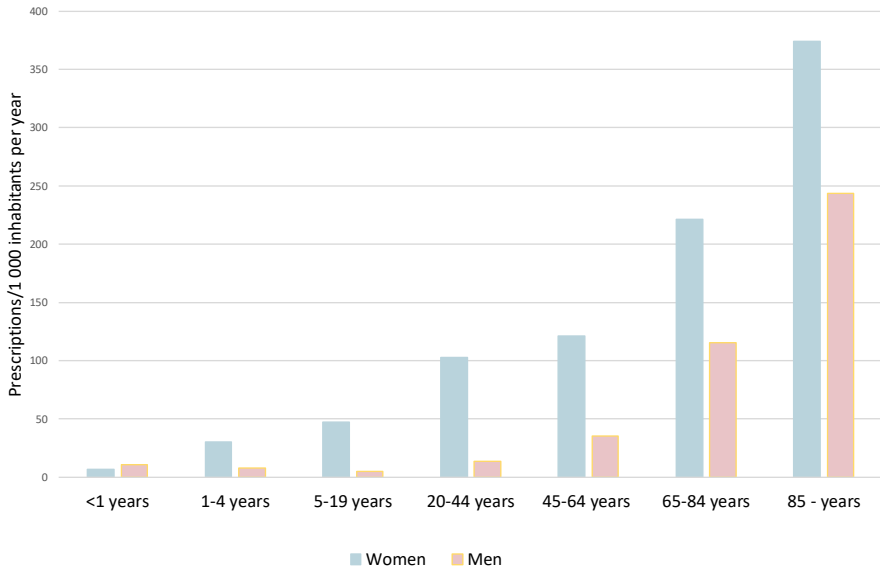
Drug	Dosage	Course length (days)
Nitrofurantoin	50 mg x 3	7
Pivmecillinam	200 mg x 3	7

*Obtain a urine sample before antibiotics are taken, and send for culture and susceptibility testing.

(source: The Medical Products Agency, Läkemedelsbehandling av urinvägsinfektioner i öppenvård-behandlingsrekommendation. 2017).

Adherence to guidelines and changes in antibiotic prescribing for urinary tract infections over time

The aim with antibiotic treatment guidelines is better and safer use of antibiotics. Studies have shown that adherence to guidelines is not always satisfactory [71, 72]. The Swedish government has set up a long-term national goal of 250 antibiotic prescriptions per 1000 inhabitants. In 2019 this number was 285 [13]. In outpatient care UTI antibiotics are the most prescribed antibiotics to women of age 70-79 years and men 80 years and older [10].



Source: the Public Health Agency of Sweden

Figure 4. Sales of antibiotics commonly used to treat urinary tract infections in year 2019. Prescriptions/1000 in humans in outpatient care. Swedres-Svarm 2018. The measure includes pivmecillinam, trimethoprim, ciprofloxacin and nitrofurantoin. (source: folkhalsomyndigheten.se)

There is a trend towards increased use of first-line antibiotics in the treatment of UTI and the overall sales of antibiotics commonly prescribed against UTI in women has decreased slowly in Sweden. Also in men sales of first-line antibiotics have increased slowly and sales of fluoroquinolones (second-line antibiotics) to men over 65 have decreased significantly in the last years [10].

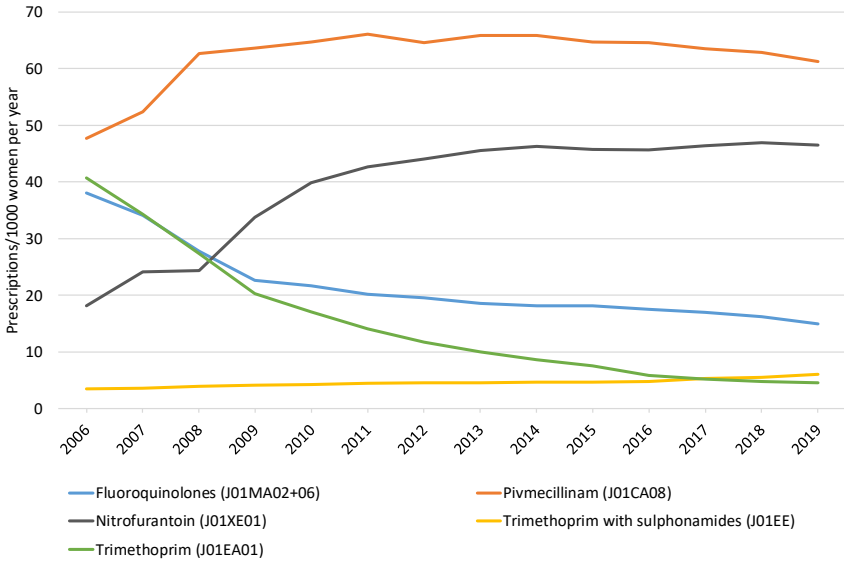


Figure 5. Sales of antibiotics commonly used to treat urinary tract infections in women, 15-79 years, 2006-2019, per year, prescriptions/1 000 women per year. (source: Socialstyrelsen.se)

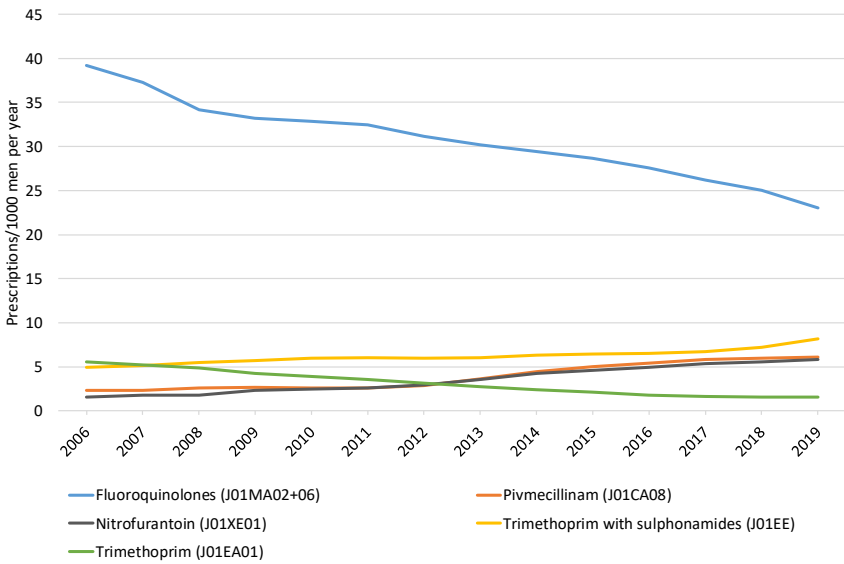


Figure 6. Sales of antibiotics commonly used to treat urinary tract infections in men, 15-79 years 2006-2019, per year, prescriptions/1 000 men per year. (source Socialstyrelsen.se)

When changing treatment guidelines, it is important to follow the quality of treatment and monitor patient outcome. One concern regarding the change towards more narrow antibiotic treatment in male UTI has been the risk of increased incidence of complications such as pyelonephritis and sepsis. So far, the few existing studies comparing narrow-with broad spectrum antibiotic treatment in male lower UTI do not show such a risk, but a tendency to more reconsultations due to recurrent UTIs [17, 73, 74].

Specific antibiotics used to treat urinary tract infection

Narrow spectrum antibiotic

Nitrofurantoin is effective against *E.coli* and *S.saprophyticus* and, in most cases, against resistant *E.coli* (ESBL-producing). The basic mechanism of action is not known but nitrofurantoin inhibits a number of microbial enzyme systems and can also damage bacterial DNA.

Pivmecillinam is a prodrug and is hydrolysed in the gut to mecillinam that is the active antimicrobial agent. Its mode of action is to inhibit bacterial cell wall synthesis in Enterobacteriales [75]. Pivmecillinam is effective against *E.coli*, *Klebsiella* and *Proteus*. Gram positive bacteria including *S. saprophyticus* are resistant in vitro but pivmecillinam is usually clinically effective against *S.saprophyticus* as high concentrations of mecillinam are achieved in the bladder.

Nitrofurantoin and pivmecillinam have little impact on the gut microbiota and are therefore less likely to contribute to the development of antibiotic resistance [3, 7]. The resistance rates for nitrofurantoin and pivmecillinam in *E.coli* from urine samples have been continuously low and were 1 and 5% respectively in 2019 [13, 76].

Broad-spectrum antibiotic

Broad spectrum antibiotics such as ciprofloxacin, trimethoprim and trimethoprim/sulfamethoxazole have high activity against gram negative bacteria. The mechanism of actions for ciprofloxacin is inhibition of replication and transcription of the bacterial DNA (through inhibition of DNA gyrase and topoisomerase). Trimethoprim and sulfamethoxazole inhibit the folic-acid metabolism in the bacteria, which inhibits the bacterial RNA and DNA. Trimethoprim and ciprofloxacin contribute to therapeutic concentrations in the prostate gland and therefore used to be the first choice antibiotics in the treatment of lower UTI in men. Unfortunately, they also cause collateral damage on gut microbiota, are related to higher rates of drug-related adverse events and contribute to the selection of drug-resistant mechanisms more than narrow-spectrum antibiotics [3, 49, 70, 77]. Swedish resistance rates to fluoroquinolones and trimethoprim in *E.coli* from urine samples were 11% and 20% respectively in 2019 [13]. Resistance rates for fluoroquinolones were highest in men 20 years and older.

According to current Swedish treatment guidelines, quinolones and trimethoprim/sulfamethoxazole should only be used in complicated UTIs or febrile UTI [7, 78].

The effect of antibiotic treatment in urinary tract infection

The purpose with empiric antibiotic treatment in uncomplicated lower UTI in women is to relieve and shorten the duration of symptoms; several studies show that treatment with antibiotics shortens the duration of symptoms [36, 37].

Median time to symptom relief when treated with antibiotics is three days [37, 79]. In an observational study, the mean duration of different symptoms after start of antibiotic treatment was 3.5 days for urinary frequency, 1.9 days for haematuria and 3.6 days for urgency [41]. In one study the median time for resolution of dysuria was three days when treated with antibiotics and five days when not treated with antibiotics [57]. In a meta-analysis involving five RCTs, women with uncomplicated lower UTI were more likely to be clinically cured when treated with antibiotics compared with placebo (61.8% versus 25.7%) [80] although adverse events were more common in patients treated with antibiotics compared with placebo. There was no significant difference between the two groups in the incidence of pyelonephritis.

Delayed antibiotic prescribing and no antibiotic treatment

Different studies have shown that more than 50% of women not being treated with antibiotics in spite of a positive urine culture, can recover without antibiotics [37, 57, 81].

In two studies including women with clinically diagnosed lower UTI, the women were willing to delay antibiotic prescribing. These women had longer duration of symptoms compared to women treated with immediate antibiotics. A large portion (23-55%) of the women did get well without antibiotic treatment, no cases of pyelonephritis were described [82, 83].

Uncomplicated UTIs are often self-limiting, 25-42% of untreated women are free from symptoms in one week [81, 84] and 31-41% will have a negative culture within a week [84]. Complications such as pyelonephritis are uncommon in this group of patients (0.5-2.6%) [36, 37].

Alternative treatments

Cranberry products are merchandised by pharmacies, are available over the counter (OTC) and used by the public to treat UTI symptoms. There are no studies indicating that cranberry products can replace antibiotics in the treatment of uncomplicated cystitis and different studies trying to evaluate the effect of cranberry products on UTI symptoms have been contradictory. A recently published meta-analysis suggests that cranberry products can be an effective non-antibiotic approach to

prevent UTI recurrence among generally healthy women [85]. Ibuprofen has also been studied in the treatment of UTI. Results have not been conclusive and there are concerns that ibuprofen could cause complications such as pyelonephritis when used instead of antibiotics in the treatment of UTI [86, 87]. Studies on symptomatic treatment with Uva-ursi (Arctostaphylos uva-ursi or bearberry) leaf extract [88], a traditional herb used to treat UTI, also available OTC, have not shown evidence of effect on frequency or severity of symptoms on UTI in women [89, 90]. Increased water intake is often suggested to patients with UTI symptoms. The clinical evidence behind this advice is sparse but in one randomised clinical study, an additional water intake of 1.5 L per day for 12 months decreased the episodes of recurrence in cystitis for included women [91]. Different studies have tried to evaluate the effect of a combination of OTC treatment and delayed antibiotic treatment, which could be a good antibiotic sparing alternative, and an opportunity for the patients to start self -medication at home before consulting [86, 89].

Urinary tract infection in primary care

As described above, UTIs are very common in primary care and in most cases are treated empirically. Patients who need treatment can be prescribed antibiotics through several different contact ways, over the telephone, via web based communication (eVisits) or at the primary health care centre (PHCC) in a face-to -face visit, when meeting a nurse (who asks the GP to prescribe antibiotics) or a GP. So far, only a few studies comparing antibiotic prescribing and outcome between eVisits and face-to -face visits in UTI in PHC have been published. These studies show different results concerning fractions of antibiotic prescribing in relation to contact type [92, 93]. The many alternative ways to present with a UTI makes it easier for the patient to get quick symptom relief but also results in fewer visits at the PHCC and makes studies more complicated to perform. Urine samples are, for example, harder to collect when patients don’t have to visit the clinic, and this could result in fewer studies on antibiotic resistance in this group of patients. If this will have implications on UTI-studies concerning antibiotic consumption and antibiotic resistance in PHC is yet to be found.

Aims

General aim

To describe UTIs in primary health care with regards to clinical symptoms, treatment outcome, antibiotic resistance antibiotic prescribing and adherence to treatment guidelines.

Specific aims

- To describe the number of consultations for patients with UTI in primary care and changes over time in antibiotic prescribing to men and women, and the adherence to treatment guidelines
- To describe antibiotic treatment, bacterial findings, the prevalence of resistant *E.coli* and factors associated with antibiotic resistance in urine cultures from patients with uncomplicated UTI in primary care.
- To describe symptoms and symptom duration in women with uncomplicated UTI in relation to bacterial growth, antibiotic treatment and specific risk factors.
- To compare the proportion of therapy failure, recurrence and complications between men diagnosed with lower UTI treated with narrow-spectrum and broad-spectrum antibiotics.

Material and Methods

Table 2. Overview of the papers

Paper	I	II	III	IV
Design	Retrospective register study	Prospective observational study	Prospective observational study	Retrospective register study
Study population	Patients registered at 88 PHCC in Sweden	Women registered at 8 PHCC in Skåne, Sweden (n=304)	Women registered at 8 PHCC in Skåne, Sweden (n= 192)	Men registered at PHCC in 5 counties in Sweden (n=16555)
Outcomes	Consultation incidence for UTI Proportion of antibiotic prescriptions	Proportion of bacterial growth in urine samples from women with uncomplicated UTI Resistance levels for *E.coli* Antibiotic treatment	Symptom description Time to recovery after consultation and factors associated with symptom duration in women with uncomplicated UTI	Incidence of therapy failure, recurrence and complications for different classes of antibiotics in men with lower UTI
Data collection period	2008, 2010, 2013	Nov 2014 to March 2016	Nov 2014 to March 2016	Jan 2012 to Dec 2015 (four counties) Dec 2012 to Dec 2015 (one county)
Data collection method	Analysis of data from the Primary Record of Infections in Sweden (PRIS)	Urine cultures with antibiotic susceptibility testing Symptom questionnaire	Symptom diary Urine cultures	Data collected from electronic medical records
Data analysis	Descriptive statistics Chi-square test	Descriptive statistics Chi-square test Binary logistic regression analysis	Descriptive statistics Chi-square test Cox regression analysis	Descriptive statistics Chi-square test Binary logistic regression analysis

Paper I

This retrospective descriptive study was based on information from the Primary Care Record of Infections in Sweden (PRIS) for the years 2008, 2010 and 2013.

The study population

To evaluate the prescribing rate and the adherence to clinical guidelines the PRIS record was created by the Unit of Research and development in Primary Care in Jönköping in 2007, supported by The Public Health Agency of Sweden. The record

consists of diagnosis-based data on infections from medical records from patients in primary health care. PHCCs joined the PRIS register on a voluntary basis. In 2008 a total of 47 PHCC with 460 529 registered persons were included in the PRIS register. An increasing number of PHCC subsequently joined the PRIS register and in 2013 a total of 88 PHCC with 785 070 registered persons were included. Included PHCC were both small and large units, private and public, situated in rural and urban areas in Sweden. All visits during office hours which resulted in a diagnosis of infection, were registered according to the international Classification of Disease and related Health Problems-Tenth Revision (ICD-10) introduced by the World Health Organization (WHO) [94]. The ATC-coding system (Anatomical Therapeutic Classification System) was used to register prescribed antibiotics. The ATC-coding system is used to classify drugs to facilitate studies on drugs in Sweden [94]. Further data recorded at each registered visit was information on the patient's identification number (encrypted ID-number), date of visit, age, sex, and, if applicable, laboratory testing were recorded.

Data processing

In purpose to describe the consultation rates and antibiotic prescribing to patients diagnosed with UTI and pyelonephritis in primary care, PRIS data from the years 2008, 2010 and 2013 were analysed with focus on visits related to UTI. All registered contacts with a diagnosis classified as UTI were included per investigated year (Appendix 1), variables retrieved were diagnosis, sex, age and prescribed antibiotic.

To calculate the number of diagnoses and antibiotic prescriptions per 1000 registered persons and year each PHCC reported the number of registered persons at their PHCC as a mean per investigated year. To calculate the incidence of UTI and prescribed antibiotics per age-group included patients were stratified in five age-groups (0-15, 16-30, 31-50, 51-70, 71- years).

Percentage of consultations due to infections, prescribed antibiotics, prescribing rate, percentage of first-choice antibiotics in women (nitrofurantoin and pivmecillinam) and proportion of patients treated for UTI from the 37 PHCCs that participated all investigated years (2008, 2010, 2013) were analysed separately and compared to that of all included PHCC. This sensitivity analysis was done to control for a possible selection bias due to additional PHCC recruited to the PRIS register each year.

Statistical analysis

All analyses were performed using Microsoft Excel and SPSS Statistics 22 (SPSS, Inc Chicago, IL). Data were mainly descriptive with numbers and frequencies presented in tables. P-values ≤ 0.05 were considered statistically significant. Differences between groups in consultation rates and antibiotic prescribing were

tested using the two-sided chi-square test for categorial variables 95% confidence intervals for ratios were reported assuming a normal distribution.

Paper II and III

The study population, paper II

A prospective observational study was performed at eight different primary health care centers (PHCC) in Skåne county, the southernmost county of Sweden with approximately 1.3 million inhabitants (2014). The selection of PHCC was performed strategically without prior understanding of antibiotic prescribing rates. Included PHCC were situated in both rural and urban areas.

Women, 17 years and older, attending the PHCC with a suspected uncomplicated UTI, (dysuria, frequent voiding or urinary urgency) were invited to participate in the study from November 1st, 2014 to the end of March 2016. Excluded patients were those with in-dwelling catheters, pyelonephritis (signs of pyelonephritis; fever ≥ 38 degrees, affected general condition with or without lower urinary tract symptoms, flank pain or renal angel tenderness) or not capable to understand and fill out a questionnaire. Clinicians were asked to treat the patients according to usual practice. All included patients were asked to fill out a questionnaire and to leave a urine sample. All patients were given a symptom diary to keep at home and fill out for a maximum of ten days.

The study population, paper III

This sub-study is based on the answers from symptom-diaries from women included in the above-mentioned study (Paper II). Inclusion criteria were women aged 17 years and older with symptoms that indicated uncomplicated UTI, capable to understand and fill out a questionnaire and without indwelling urinary-catheters or signs of pyelonephritis. Patients were asked to fill out a questionnaire regarding previous UTI history and a symptom diary. Only patients with completed symptom diaries and analysed urine cultures were included in this study.

Questionnaire

Patients recorded baseline symptoms graded from 0 to 3 (no symptoms, mild symptoms, quite much symptoms, very much symptoms), age, former antibiotic treatment, former and current UTIs, self-medication prior to visit, recent travels abroad and if they were prescribed antibiotics, the name of the antibiotic. Questions were based on relevant symptoms and factors known to influence symptom duration, antibiotic resistance and from questionnaires used in former studies [41, 95]. The questionnaire was pilot-tested with patients and smaller changes were done before the onset of the study. Patients were asked to fill out the questionnaire before

leaving the PHCC (Appendix 2). If information regarding antibiotic prescribing was missing, this information was retrieved from the electronic medical record by the researcher.

Symptom diary

Included patients were asked to fill out a paper diary describing daily symptoms graded from 0 to 5 (no symptoms, almost no, slight, moderately bad, bad, very bad symptoms) for a maximum of ten days after consultation (Paper III). Included symptoms represent common complaints from patients visiting with symptoms indicating uncomplicated UTI (dysuria, frequency, urge, stomach ache, smelly urine). The patients were also asked to describe restrictions in daily activities and sick-leave (Appendix 3).

The diary was returned in a pre-paid envelope and patients were reminded with a text-message (SMS) after one week. If the diary still wasn't returned after the first SMS another SMS was sent as a reminder after two weeks.

Data processing, symptom diary

In the presentation of results "any symptom" is defined as symptoms graded as slight symptoms or more (grading 2-5). Time to symptom resolution was defined as when the self-reported symptom scores were scored as almost no symptoms or less (grading 0 and 1). The variable age was dichotomized into 17 to 50 years and 50 years and older, representing premenopausal and postmenopausal women. For each question in the diary the internal drop-out was 4-5% (Paper III).

Urine sample and bacterial analysis

A urine sample was collected from all included patients, stored at +4 degrees and sent to the Department of Laboratory Medicine, Division of Clinical Microbiology in Lund for microbiological analysis and susceptibility testing on the day of collection. Identification to the species level was performed by using approved conventional methods [52]. Growth of bacteria was considered significant if the number of colony-forming units (CFU)/mL was $\geq 10^3$ for primary pathogens as *E.coli* and *S.saprophyticus* and $\geq 10^4$ (CFU)/mL for secondary pathogens [7]. Antimicrobial susceptibility testing followed guidelines on breakpoints proposed by the European Committee on Antimicrobial Susceptibility testing (EUCAST) [96]. *E.coli, Klebsiella pneumoniae* or *Proteus mirabilis* resistant to cefotaxime and/or ceftazidime were confirmed as ESBL- producing bacteria by the MAST test (MAST UK) [97]. Strains with reduced susceptibility to carbapenems were examined with Check MDR (https://check-pointshealth.com/epidemiology/). Patients were only included in the study once.

Dipstick urinalysis was performed at the PHCC according to the manufacturer's instructions (Combur-test 7®). In this study parameters considered in dipstick

analysis were nitrites and leukocyte esterase. Cut off values for a positive result were 1+ or more for leukocytes.

Statistical analysis

Questionnaire and laboratory data were collected in Microsoft Excel and statistical analysis was performed using SPSS 22.0 software (Paper II) SPSS 25.0 (Paper III) (IBM Armonk, NY, USA). Statistical tests used were 2-tailed and p-values <0.05 were regarded as significant.

The chi-square test was used to compare proportions on categorical data (Fishers' exact test was used for small sample sizes). Mann-Whitney U-test was used for continuous variables. Binary logistic regression was used to model the correlation between antibiotic resistance in *E.coli* and several independent variables (Paper II). Odds ratios (OR) with 95% CI were calculated.

Cox-regression analysis was used to identify the influence of patient anamnestic factors, antibiotic treatment, results from urine cultures and time to symptom resolution (calculated in hazard ratios expressed as relative risks (RR) and 95% confidence intervals) (Paper III). Variables with p-values <0.10 were used in the multiple Cox-regression analysis (Paper III).

Paper IV

This retrospective study was based on information derived from electronic medical records (EMR) in five different Swedish counties with a total population of 883 449 men in 2012 and 909 069 men in 2015.

The study population

Men from 289 PHCC and 20 hospitals situated in five different counties in southern and central Sweden were included. Through electronic medical record databases of Jönköping, Kalmar, Kronoberg, Skåne and Uppsala county, data for all men aged 18-79 years diagnosed with lower UTI or complications to UTI in PHC and hospital care were identified. From four counties data were retrieved from January 2012 to December 2015. For one county the data were collected from December 2012 to December 2015 and from this county no data on index visits from hospitals were retrieved. Data on day of consultation, diagnosis, antibiotic treatment, urine dip-stick, C-reactive protein (CRP) and results from urine cultures were extracted. Microbiological analyses were performed at five different laboratories, one in each county, all used the same approved conventional methods of the identification to the species level.

Data processing

Patients eligible for the study were men with a visit in PHC or hospital care and an ICD code indicating lower UTI in connection with an antibiotic prescription (Appendix 4). UTI episodes with an antibiotic prescription in the preceding 30 days were excluded. No visits during the first 30 days of the study were included due to lack of information about antibiotic prescribing preceding the start of the study. The study started on January 1, 2012 in four of the five included counties. In Skåne county the study started on December 8, 2012. Index visits were included until December 31, 2015. The follow-up period after an index visit was for a maximum of 35 days after an index UTI visit.

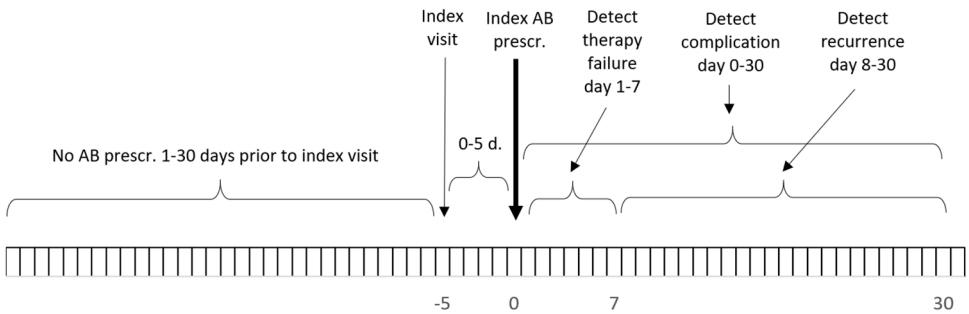


Figure 7. Observation time Definitions**. Index visit**: No antibiotic prescription within the preceding 30 days. **Index antibiotic prescrition:** Should take place within five days from the index visit (if a urine culture is to be analysed prior to antibiotic prescribing it might take up to five days from the index visit to the index antibiotic prescription). **Therapy failiure**: May be detected within day 1-7- from the index antibiotic prescription. **Recurrence**: May be detected within day 8-30 from the index antibiotic prescription **Complication**: May be detected within 30 days from the index antibiotic prescription.

Prescribed antibiotics were registered according to the Anatomical Therapeutic Classification System (ATC). Antibiotics intended to be further analysed in the study were divided into three different groups, broad spectrum antibiotics, long-term ≥10 days (ciprofloxacin, trimethoprim/sulfamethoxazole), broad-spectrum short term <10 days (trimethoprim), and narrow spectrum antibiotics (nitrofurantoin, pivmecillinam). Therapy failure was defined as a new prescription of a new relevant UTI antibiotic within seven days from index antibiotic prescription and a new registered lower UTI diagnosis. Recurrence was defined as a new visit 8≤d≤30 days from the index antibiotic prescription in combination with a lower UTI diagnosis and an antibiotic prescription. Any complication was defined as a revisit in PHC or hospital care combined with a complication diagnosis (pyelonephritis, sepsis) and an antibiotic prescription or antibiotic treatment (if hospitalised) within 30 days from the index antibiotic prescription.

Statistical analysis

The data collected in the study were analysed using Matlab 2019a (Matworks, Natick, MA), Excel 2016 (Microsoft Corp, Redmond, WA, USA) and SPSS Statistics 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0 Armonk, NY IBM Corp).

Statistical significance was set at $p<0.05$ (two-sided).

Comparison between proportions of categorical variables in two independent groups was performed with the two sided chi-square test.

Binary logistic regression was used to model the correlation between therapy failure, recurrence and complications and antibiotic choice and other independent variables. Odds ratios (OR) with 95% CI were calculated.

Ethical considerations

All studies have been approved by the Regional Ethical Review Boards in Linköping (Paper I) and Lund (Paper II-IV).

Ethical considerations for Paper I

Confidentiality for patients was ensured by using a one-way encrypted ID-number. Ethical approval for the PRIS register was obtained from the Regional Ethical Review Board in Linköping, Sweden. Case number 2010/227-31.

Ethical considerations for Paper II and III

Informed written consent was obtained from all participants and included patients could withdraw from the study at any time. The data was pseudonymised before the analysis and could not be linked to any participant. Ethical approval was obtained from the Regional Ethical Review Board in Lund. Case number 2014/432.

Ethical considerations for Paper IV

Confidentiality for patients was ensured by using an encrypted ID number. The study was approved by the Regional Ethical Review Board in Lund. Case number 2016/462.

Results

Main findings

There was a slight increase in consultation rates for lower UTI between the years 2008 and 2013. During these years there was an increase in the use of recommended narrow-spectrum antibiotics (nitrofurantoin and pivmecillinam) to treat lower UTI in women and men while prescriptions of broad-spectrum antibiotics (trimethoprim and ciprofloxacin) decreased for both men and women (Paper I).

Antibiotic resistance in *E.coli* was low in isolates from women attending PHC with symptoms indicating uncomplicated UTI and resistance rates for ciprofloxacin were lower than reported from the local clinical laboratory. Antibiotic treatment within the last year was independently associated with antibiotic resistance in *E.coli* (Paper II).

Women with UTI symptoms attended PHC after a median symptom duration of four days. Three quarters of the patients reported restrictions in daily life due to UTI symptoms and the median number of days with any UTI symptom after visit at the PHCC was four days when treated with antibiotics and 6.5 days when not treated with antibiotics (Paper III).

During the four studied years (2012-2015) ciprofloxacin was the most frequently prescribed antibiotic to men diagnosed with lower UTI, prescribed in 52% of the cases. There was no difference in the incidence of complications between patients treated with broad- or narrow-spectrum antibiotics, but therapy failure and recurrence were more common in patients treated with nitrofurantoin, pivmecillinam and trimethoprim as compared to ciprofloxacin (Paper V).

Adherence to treatment guidelines in patients with urinary tract infection (Paper I)

Antibiotic prescribing and lower urinary tract infection

The number of antibiotic prescriptions due to UTI per registered woman was 60/1000 in 2008, 63/1000 in 2010 and 58/1000 in 2013. The number of antibiotic prescriptions due to UTI in men was much lower than in women and was 7/1000 in

2010 and 2013, and 8/1000 registered men in 2013. The number of women with lower UTI, who were prescribed pivmecillinam and nitrofurantoin, increased from 54% in 2008 to 69% in 2013. The proportion of trimethoprim or fluoroquinolones prescribed to women decreased from 24% in 2008 to 7% in 2013. For men, the proportion of pivmecillinam or nitrofurantoin increased from 13% in 2008 to 31% in 2013 while the proportion of prescribed trimethoprim and fluoroquinolones decreased from 54% in 2008 to 32% in 2013.

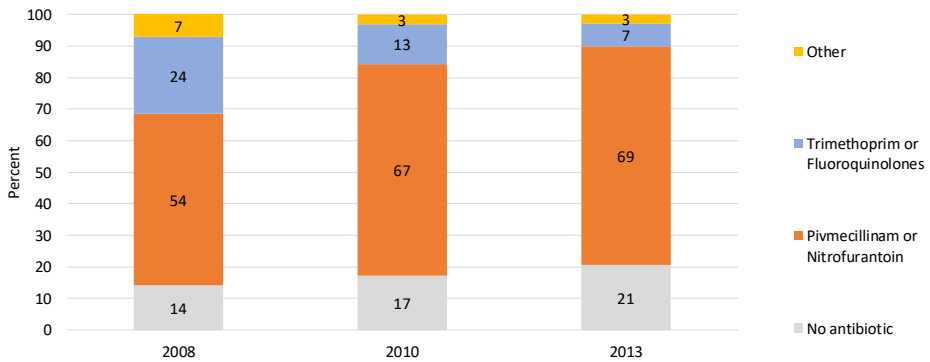


Figure 8. PRIS data. Proportion of antibiotic prescriptions in women of all ages, diagnosed with lower UTI

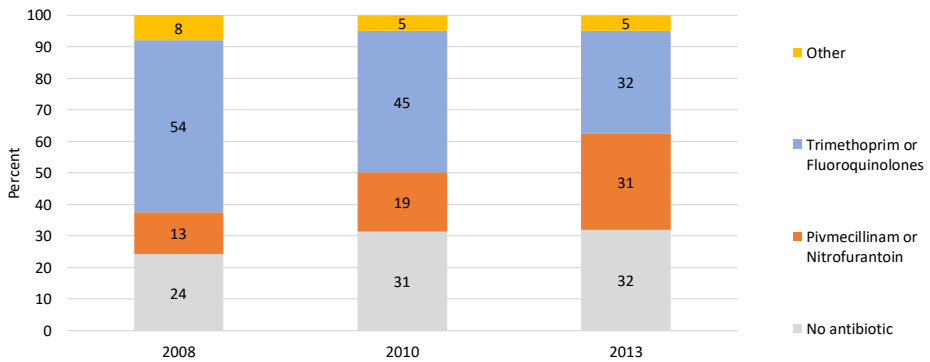


Figure 9. PRIS data. Proportion of antibiotic prescriptions in men of all ages, diagnosed with lower UTI

Lower UTI was most common in women 71 years and older, it was uncommon in men younger than 50 years, the incidence increased thereafter with age but was still far less common than in women.

The fraction given no antibiotic despite a UTI diagnosis increased for both men and women during the investigated years from 14% in 2008 to 20.5% in 2013 for women and from 24% for men in 2008 to 32% in 2013.

Antibiotic prescribing and pyelonephritis

Fluoroquinolones were the most common antibiotics prescribed to both women and men diagnosed with pyelonephritis. Pyelonephritis was far less common than lower UTI, consultation rates for women and men were stable during investigated years and were 1.9/1000 registered women and 0.8/1000 registered men in 2013.

Uncomplicated urinary tract infection, women in primary health care; etiology, resistance and treatment (Paper II)

In total 324 women accepted to participate in the study, 304 of these women had urine samples analysed and were included in the final presentation of data. The included 304 women had a median age of 46 (IQR 32-66) years. The median number of days of symptom duration at visit was four (IQR 2-7) and median bladder incubation time was 2.5 (IQR 1.2-4) hours. A total of 55 patients (17%) had been abroad within the last six months. Bacterial growth was found in 243 (80%) of urine samples. *E.coli* and *S saprophyticus* were the most common pathogens and were found in 72% and 9% of the positive urine samples. The remaining urine cultures were other Gram-positive species 7%, other Gram-negative species 5%, *Streptococcus group B* (4%) and other 2%.

Urine dipsticks

A total of 298 women were examined with both dipstick and urine culture. In samples with any bacterial growth dipstick tests were positive for nitrite in 32% and for leukocyte esterase in 79%. In samples with growth of *E.coli* dipstick tests were positive for nitrite in 40% and for leukocyte esterase in 85%. In samples with no growth of bacteria, dipstick detected nitrite in 5% and leukocytes in 49%. The positive predictive value (PPV) for growth of any bacteria when nitrite in dipstick test was positive was 97%. The negative predictive value (NPV) was 27%. Corresponding figures for positive leukocyte esterase test were PPV 86% and NPV 39%.

Antibiotic resistance in *E.coli* isolates-comparison with data on antibiotic resistance from the local clinical laboratory of microbiology

In total 80% of detected *E.coli* isolates were susceptible to all tested antimicrobials. A difference in the prevalence of *E.coli* isolates resistant to ciprofloxacin between

isolates collected in the study and isolates reported from the local clinical microbiology laboratory for the same time-period and age-group was found. This difference was not observed for the other antibiotic groups (Table 3).

Table 3. Comparison of antibiotic resistance for Escherichia coli in the study and in routine laboratory data[a] (women 17 years and older)

Antibiotic tested/resistance mechanism	Resistance in primary care No of samples n (%) (n=176)	Resistance reported from the laboratory[b] No of samples n (%) (n=23 179)	p-value
Mecillinam	2 (1.1)	714 (3.1)	0.18[c]
Nitrofurantoin	0 (0)	184 (0.8)	0.66[c]
Trimethoprim	30 (17.0)	4612 (19.9)	0.35[d]
Cefadroxil	4 (2.3)	1223 (5.3)	0.087[c]
Ciprofloxacin	2 (1.1)	1400 (6.0)	0.0022[c]
ESBL-producing	4 (2.3)	807 (3.5)	0.53[c]

[a]Urine samples from women during November 2014 to March 2016
[b]The Department of laboratory medicine, Division of Clinical Microbiology in Lund
[c]The Fisher exact text
[d]Chi-square test

Factors of importance for antibiotic resistance

Treatment with UTI antibiotics within the last 12 months was associated with increased odds for antibiotic resistance in *E.coli* (adjusted OR 4.97 95% CI 2.04-12.06). Travelling abroad within the last six months increased the odds for resistant *E.coli* (adjusted OR 4.02 95% CI 1.35-11.35). No association between antibiotic resistance and the number of antibiotic prescriptions the last year, age, incontinence or diabetes was found.

Antibiotic treatment

A total of 74% of the women were prescribed antibiotics empirically. Pivmecillinam was the most common prescribed antibiotic prescribed to more than 50% of the patients who were prescribed antibiotics. Appropriate antibiotics were prescribed to 73% of the women (patients with growth of bacteria sensitive to the prescribed antibiotic and patients with no growth of bacteria not prescribed antibiotics). To 49% of patients with a culture negative for UTI antibiotics were prescribed non-concordantly. 14% of patients with growth of bacteria were not prescribed antibiotics.

Table 4. Empiric antibiotic treatment of uncomplicated urinary tract infection in women

Antibiotictreatment	n (%)
Any antibiotc	225 (74.0)
Pivmecillinam	124 (55.1)
Nitrofurantoin	86 (38.2)
Trimethoprim	5 (2.2)
Ciprofloxacin	5 (2.2)
Other[a]	5 (2.2)

[a]Cefadroxil, Trimethoprim/sulfamethoxazole, Doxycycline

Presentation and clinical outcome of urinary tract infection, women in primary health care (Paper III)

Symptoms at first visit

A total of 324 women with symptoms of uncomplicated UTI agreed to participate in the original study (Paper II). Of those, 20 had missing urine cultures and 112 did not return their symptom diaries. We included the 192 women with both completed symptom diaries and analysed urine cultures. Patients that returned diaries were older, were to a higher extent prescribed antibiotics, had more frequent bacterial growth in urine and were less restricted in daily activities than women that did not return the diaries.

The median age among the included women was 51 years (IQR 35.0-69.0). The most common symptoms reported were frequency (94%), urgency (93%), dysuria (88%) and painful micturition (81%). Urge and frequency were described as the most severe symptoms. Stomach ache was reported by almost half of the patients. There was no difference in symptom severity between women, with and without bacterial growth in urine culture, except for the symptom “painful micturition” which was graded as quite much and much symptoms more often in patients with bacterial growth as compared with patients without bacterial growth in urine culture. Visible blood in urine was reported by 24% of patients with bacterial growth and 10% of patients with no growth in urine culture. Irrespective of bacterial growth, restrictions in daily life related to UTI symptoms were reported by 74%.

Self-medication products prior to visit were consumed by 63% of the women where cranberry products were most popular, consumed by 56% (Table 5).

Table 5. Reported use of home remedies in questionnaire

	Home remedy, n=118	No home remedy, n= 69
Age (Median (IQR)	50 (35-67)	56 (38-73)
Number of days with symptoms before consulting (Median (IQR))	4.0 (3.0-5.0)	4.0 (3.0-7.0)
Prescription of antibiotics, n(%)	97 (82.2)	55 (80.9)
Growth of bacteria in culture, n (%)	99 (83.9)	58 (84.1)
Home remedy product		
Cranberry products, n (%)	66 (55.9)	
Painkiller, n (%)	12 (10.2)	
Plenty of liquids, n (%)	48 (40.7)	
Other herbal products, n (%)	3 (2.5)	

*5 patients did not answer the question. Some patients reported more than one home remedy.

Microbiology

In 83% of urine cultures bacterial growth was detected; Enterobacteriales dominated by *E.coli* were found in 76% of positive cultures. Antibiotic resistance in *E.coli* was low, except for trimethoprim for which 15% were resistant.

Recovery

The median time to recovery after consultation was, irrespective of bacterial growth, four days for all women treated with antibiotics and 6.5 days for all not treated with antibiotics (p=0.004).

Antibiotic treatment was associated with shorter symptom duration (RR 0.47 95% CI 0.27-0.81). Age > 50 years was associated with longer duration of symptoms after consultation (RR 1.76 95% CI 1.25-2.49). No association was found between duration of symptoms reported in the symptom diary and the independent variables diabetes, incontinence, recurrent UTIs, higher than median symptom score at inclusion, growth of bacteria, antibiotic resistance and UTI antibiotic treatment last month (Table 6).

Table 6. Factors associated with duration of symptoms registered in symptom diary*

	Univariate model		Multiple model	
	Relative risk RR (95% CI)	**p-value**	**Relative risk RR (95% CI)**	***p*-value**
Age >50 years	1.73 (1.22-2.46)	0.002	1.76 (1.25-2.49)	0.001
Diabetes	1.02 (0.47-2.18)	0.96		
Incontinence	1.14 (0.47 -2.80)	0.77		
Recurrent UTI**	1.53 (0.82-2.84)	0.18		
Symptom score at inclusion***	0.97 (0.69-1.38)	0.89		
No growth of bacteria in urine culture	Reference			
Growth of bacteria without antibiotic resistance	0.62 (0.34 -1.14)	0.12		
Growth of bacteria with ab resistance	1.12 (0.74-1.69)	0.60		
Antibiotic treatment at consultation	0.54 (0.32-0.90)	0.02	0.47 (0.27-0.81)	0.006
UTI antibiotic treatment last month	1.98 (0.97-4.06)	0.06	1.78 (0.90-3.51)	0.097

*Women with suspected lower urinary tract infection: Univariate and multiple Cox regression analysis, calculated in hazard ratios, expressed as relative risk and 95% confidence intervals. Variables with *p*-values <0.10 (age>50, antibiotic treatment at consultation and UTI antibiotic treatment last month) were used in the multiple Cox regression analysis.

**Recurrent UTI=≥2 infections in six months or ≥3 infections in one year.

***) Symptom score at inclusion: A total symptom score at inclusion was calculated by adding the dichotomized (0,1=0, 2,3 =1) symptom scores for the symptoms dysuria, painful micturition, frequency, incontinence and urge. The median baseline symptom score at inclusion was calculated. The median symptom score at inclusion was then used to dichotomize the symptom score at inclusion in higher and lower than median total symptom score at inclusion.

CI= Confidence interval

Different antibiotic regimes in men diagnosed with urinary tract infection-a retrospective register-based study (Paper IV)

During the investigated years (2012-2015) a total number of 44 612 visits diagnosed as lower UTI with a concurrent prescription of antibiotics among men aged 18-79 years were made in the five participating counties. Of these diagnoses 22 999 met the inclusion criteria for a correct index visit. Relevant antibiotics were prescribed in 21124 of these visits and were thus included in the final study.

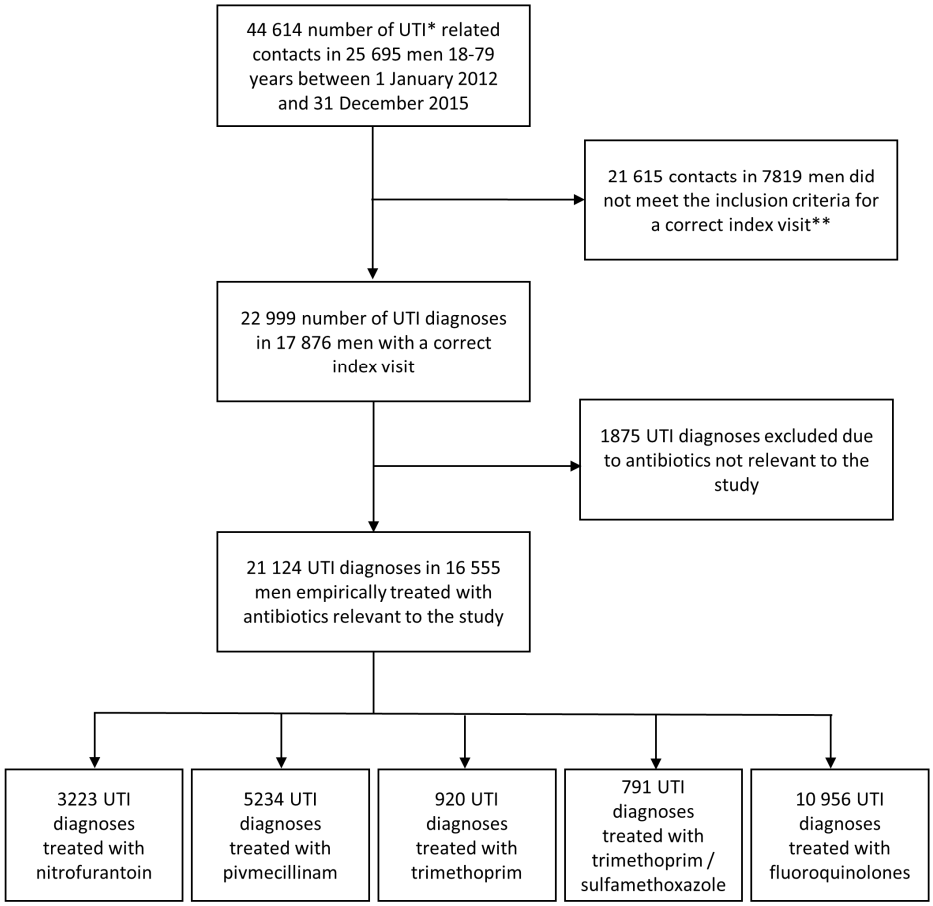


Figure 10. Flow chart of the inclusion process
*UTI:Urinary tract infection
** Inclusion criteria:Inclusion criteria were age 18-79 years (<80) and an index visit to primary health care or hospital combined with a defined diagnosis of lower UTI, a prescription of UTI antibiotics on the day of visit or within five days from the consultation.

The median age of included patients was 65.0 IQR (51-72) years. 78% of the patients were handled in PHC.

Identification of bacteria

Urine cultures were analysed for 11 655 (55%) of the patients, the analysis result dates were matched on day 0 to day 5 from index visit. The most common bacteria was *E.coli* and was detected in 3529 of the urine cultures (30%) followed by *Klebsiella* species 446 (4%) and *Enterococcus* species 402 (3%). In 2066 (18%) other single pathogens were found and in 805 (7%) mixed growth was reported. In 4387 (38%) samples no growth of bacteria was found.

Antibiotic treatment

The most frequently prescribed antibiotic was ciprofloxacin, prescribed in 10 956 cases (52%) (Table 7).

Table 7. Antibiotic prescribing

Antibiotic	Number (%)
Pivmecillinam	5234 (25)
Nitrofurantoin	3223 (15)
Trimethoprim	920 (4.3)
Trimethoprim/sulfamethoxazole	791 (3.7)
Ciprofloxacin	10956 (52)
Total	21 124

Therapy failure, recurrence and complications

Reconsultations due to therapy failure and recurrence were detected in 192 (0.9%) and 1277 (6%) cases respectively. Complications within 30 days from index antibiotic prescribing was registered in 121 (0.6%) cases, 99 (82%) of these cases were pyelonephritis and 22 (18%) were sepsis. Therapy failure and recurrence were more common in patients treated with pivmecillinam, nitrofurantoin and trimethoprim as compared to the broad spectrum antibiotics ciprofloxacin and trimethoprim/sulfamethoxazole. This difference was not found regarding complications (Table 8).

Table 8. Therapy failure and complications in relation to prescribed index antibiotic

	Narrow spectrum antibiotic[1] n=8457 n(%)	Broad-spectrum antibiotic[2]<10 days n=920 n(%)	p-value[3]	Broad-spectrum antibiotic[4]≥10 days n=11747 n(%)	p-value[5]
Therapy failure	103 (1.2)	11 (1.2)	0.92	78 (0.7)	<0.001
Recurrence	779 (9.2)	61 (6.6)	0.02	437 (3.7)	<0.001
Complication	45 (0.5)	4 (0.4)	0.89	72 (0.6)	0.48

p-values were calculated using the chi-square test
1. Pivmecillinam, nitrofurantoin
2. Trimethoprim
3. Comparison between narrow spectrum and broad-spectrum antibiotic<10 days (trimethoprim)
4. Ciprofloxacin, trimethoprim/sulfamethoxazole
5. Comparison between narrow-and broad-spectrum antibiotics≥10 days (ciprofloxacin, trimethoprim/sulfamethoxazole)

There was an association between a raised crp level (>20 mg/L) at index visit and complications, this association was not found regarding recurrence and therapy failure (Table 9). Age over 55 years was associated with therapy failure, recurrence and complications (Table 9)

Table 9. Risk factors for therapy failure, recurrence and complications

	Therapy failure n=192		Recurrence n=1277		Complications n=121	
	Crude OR (95% CI)	Adjusted[1]OR (95% CI)	Crude OR (95% CI)	Adjusted[1]OR (95% CI)	Crude OR (95% CI)	Adjusted[1]OR (95% CI)
Age over 55 years	1.6 (1.1-2.3)	1.6 (1.2-2.3)	1.6 (1.4-1.9)	1.7 (1.5-2.0)	1.9 (1.2-2.9)	1.7 (1.1-2.7)
CRP≥20 mg/L	1.1 (0.8-1.5)	1.4 (1.0-1.9)	0.7 (0.6-0.9)	1.0 (0.9-1.2)	2.7 (1.9-3.9)	2.8 (1.9-4.1)
Broad-spectrum ab≥10d	Ref	Ref	Ref	Ref	Ref	Ref
Broad-spectrum ab<10d	1.8 (1.0-3.4)	1.9 (1.0-3.7)	1.8 (1.4-2.4)	1.9 (1.4-2.5)	0.7 (0.3-1.9)	0.9 (0.3-2.5)
Narrow-spectrum ab <10d	1.8 (1.4-2.5)	2.0 (1.5-2.8)	2.6 (2.3-3.0)	2.7 (2.4-3.1)	0.9 (0.6-1.3)	1.2 (0.8-1.8)

Abbreviations: CI, confidence interval; OR, odds ratio; CRP, C-reactive protein; Narrow-spectrum antibiotic, pivmecillinam or nitrofurantoin; Broad-spectrum antibiotic treatment<10 days, trimethoprim; Broad-spectrum antibiotic ≥10 days, trimethoprim/sulfamethoxazole or ciprofloxacin. Missing cases, CRP 12345 (58.4%). 1,Method: Log regression-enter, adjusted for age, CRP, narrow-spectrum antibiotic, broad spectrum antibiotic<10 days and broad-spectrum antibiotic≥10 days treatment. Broad- spectrum antibiotic ≥10 days was used as reference.

The start-date for data collection from all counties except Skåne was January 2012. Data extraction from Skåne started in December 2012. Index visits from hospitals were included for all counties except Skåne. A sensitivity analysis was done to control for possible selection bias for Skåne county. Data from the four counties with data from January 2012 to December 2015 were compared with the data from Skåne regarding percentage of revisits due to therapy failure, recurrence and complications and antibiotic choice. No difference between the groups was found.

Discussion

Main findings

This thesis shows that *E.coli* were the most common bacteria in urine cultures from women that consulted primary care with UTI symptoms, resistance levels in *E.coli* to commonly used UTI antibiotics were low except for trimethoprim. The level of resistance to ciprofloxacin in *E.coli* from women with uncomplicated UTI in PHC was lower than in routine laboratory data. We also found that women were feeling bad and restricted in daily activities for several days before and after consulting because of UTI symptoms, and they often tried to relieve symptoms with self-medication products. Antibiotic prescriptions were to a large extent adherent to clinical guidelines, even though rates of prescriptions of UTI antibiotics to older patients were high and ciprofloxacin was the most prescribed antibiotic in male lower UTI patients. UTIs were uncommon in men-and complications within 30 days from a diagnosis of lower UTI in men were rare, irrespective of narrow -or broad-spectrum antibiotic choice at index visit.

Methodological considerations

Design

In order to assess whether antibiotics are used adequately, diagnosis linked prescription data from PHC is needed. The strength with Paper I is the diagnosis linked prescription data from the PRIS record. With data from the record, we were able to objectively describe the incidence of lower UTI and pyelonephritis and the prescription rate of antibiotics to this group of patients in PHC. Previous studies conducted in Sweden on prescribing in PHC were mainly based on sales data. In 2013 a total of 88 PHC from different parts of Sweden were included in the PRIS register, with a total population of 785 070 registered persons. In 2013 the population in PRIS represented 8% of Sweden's population; the results can therefore be generalised to the population of Sweden.

During the three investigated years an increasing number of PHCC joined the PRIS register, from 47 in 2008 to 88 in 2013, which could affect the results. We did a

sensitivity analysis and did not find any difference between the PHCC that participated all years and the total number of PHCCs.

The PHCCs were registered to PRIS on a voluntary basis, which might be a limitation. PHCCs more interested in monitoring their prescribing could be more interested in joining the register. The included PHCCs were situated in different counties of Sweden, in both urban and rural areas, both high and low prescribing units were registered as well as private and public, which should minimise this risk. The PRIS register did not include visits during after office-hours thus the number of visits for UTIs in primary care as well as antibiotic prescriptions could have been underestimated.

Limitations with register-based studies are that we are dependent on clinicians registering the correct diagnosis when prescribing antibiotics, and we do not have the same possibility to control for different individual factors as in smaller clinical studies. We do not know if the patient did take the antibiotic prescribed. In PHC patients are often treated empirically with antibiotics and it could be that a diagnosis is chosen to justify the antibiotic prescription. The Swedish remuneration model for primary health care is partly based on compensation for registered diagnosis, which could be an incentive for the GPs to register more UTI diagnosis in cases of uncertainty. To minimise the risk of invalid UTI diagnosis (Paper IV), we used defined criteria for inclusion and we only included registered index episodes with adjacent antibiotics prescription date within five days after consultation. We also excluded all cases that had an antibiotic prescription within 30 days prior to the index visit. Another limitation with the register-based studies is the lack of information about the patients regarding co-morbidities, socioeconomic status and other actual symptoms. In Paper IV we observed that patients prescribed ciprofloxacin and trimethoprim/sulfamethoxazole had higher levels of CRP at index visit. This could indicate that these patients were more affected from the beginning. Individual patient factors can cause selection bias (confounding by indication) and, especially in Paper IV, better knowledge of these factors would make it possible to compute a propensity score (meaning the predicted probability of the use of a specific therapy over another based on, for example, socioeconomic and anamnestic factors).

In the observational prospective studies (Paper II and III) the study design was aimed to be as similar to routine clinical practice as possible. To interfere with the GPs antibiotic prescribing as little as possible, patients instead of GPs were asked to register prescribed antibiotics in the questionnaire. The symptoms were based on the common presenting symptoms of UTI. The response rate regarding the questionnaire was high, the quality of the answers was high and the internal drop-out was low. A total of 62% of women returned their diaries. Other researchers have previously reported both higher and lower answering rates for symptom diaries (49-71%) [40, 41, 98]. Participants that returned the diary were, in general older, had longer symptom duration before seeking care and received antibiotic treatment to a

higher extent than patients that did not return the diaries. A response bias could interfere with the results and this is important to have in mind when interpreting the results from the study. Symptom diaries are common in UTI studies, the method has formerly been validated [83, 98-100]. The specific score used in our diary was not validated, some of the symptoms asked for (questions regarding dysuria, frequency and urgency) were the same as the cardinal symptoms used in routine clinical practice (Paper III). We were not able to find a validated symptom diary for UTI symptoms in Swedish. Further studies are needed to develop a diary applicable to the Swedish PHC context, which measures patient experience of symptoms and recovery, and with validated questions and scoring.

In the clinical study (Paper II) the aim was to recruit 400 patients in order to collect 200 *E.coli* samples, which we estimated would be enough to calculate the prevalence of resistant *E.coli*. In practice, clinicians were not able to recruit the number of patients stipulated even though the recruitment period was extended. The study was terminated after 17 months due to changed conditions at the PHCCs, which made it difficult to continue the inclusion of patients. The study did not interfere with the treatment and it is unlikely that any bias would occur as a consequence of exclusion of specific patient characteristics. All patients in the study were included in relation to a clinical visit at the PHCC, either to a nurse guided by a specific UTI decision aid or a physician. All prescriptions were done by physicians.

The PHCCs included in the study were chosen strategically with no former knowledge about UTI incidence and antibiotic prescribing. The centres were situated in both urban and rural parts of Skåne, and both private and public PHCC were included. Based on this we consider that the sample is representative for the population of women with UTI in Sweden (Paper II and III).

There are only a few studies conducted on men with lower UTI in primary care. The infection is much less common in men than in women and therefore harder to study. With the two register-based studies, we could follow a large population of men and were able to analyse the actual incidence of lower UTI and pyelonephritis (Paper I and IV). In order to follow a population of men diagnosed with lower UTI, regarding reconsultations and complications, we gathered data from electronic medical records on antibiotic prescribing, diagnosis and urine cultures from five different counties (Paper IV). The medical record systems are different in different counties and, in some counties, they are separated in different registers depending on the level of care. In one county (Skåne), we were not able to retrieve index visits for UTIs from hospitals and the start date for inclusion of the county of Skåne was 11 months later than the rest of the counties. This could cause selection bias and thus we compared the outcome measures for Skåne and the counties with complete data and found no difference between antibiotic treatment, the incidence of therapy failure, recurrence and complications.

The UTI diagnosis

Cultures-diagnostic methods primary care

An accurate diagnosis of uncomplicated UTI is desirable before onset of treatment. Unfortunately, there is no perfect and quick method to diagnose a UTI. Patients with UTI are treated empirically, meaning that the therapy is based on experience and directed against an anticipated cause of infection, taking into account the risk for presence of drug resistant strains.

Studies from women attending PHC, with symptoms indicating a UTI, show that only 50-80% of the women have a UTI according to gold standard (urine culture with growth of bacteria in combination with clinical symptoms) [48]. The cut-off for a positive urine culture is based on studies from Kass in the 1950's and later Stamm [101]. In several studies the researchers have tried to evaluate the optimal diagnostic methods including, for example, urine dipsticks, algorithms for combination of symptoms and anamnestic factors sometimes including urine dipsticks, urine sediments (microscopy) and urine dip slides [48, 51, 55-57, 102-104]. The studies show different results and no single specific anamnestic or clinical sign can predict or rule out a UTI but a urine dipstick positive for nitrite or moderate pyuria can predict the condition [103, 104]. In Sweden, urine dipsticks are commonly used as a point-of-care test (POC-test) to find urine samples with bacterial growth by analysing leukocytes and nitrite in the urine. Results from urine dipsticks performed on urine samples analysed in Paper II (unpublished data) show a positive predictive value (PPV) of 97% for growth of any bacteria when the nitrite test was positive. The negative predictive value (NPV) was 26%. The figures regarding PPV for nitrite test correspond well with previous Swedish studies conducted in primary care settings [51, 105]. The NPV in our study was even lower than in previous studies. The NPV for a test decreases when the pre-test probability for a positive result increases, which could be the case in our study where 80% of included women had positive urine cultures. Since the NPV for dipsticks is low, a UTI cannot be ruled out with a negative nitrite test. In paper IV we describe that in around 50% of the included men urine dipsticks and urine cultures were analysed thus showing that urine dipsticks are popular and are used as a routine POC-test in clinical practice.

A bladder incubation time of four hours (or a specimen over a night's bed rest) has been traditionally recommended as the urine will get more concentrated and the incubation time will allow for the bacteria to grow. The time is recommended to get the highest sensitivities [101]. In Paper III bladder incubation time for women was 2.0 hours for patients with no growth and 3.0 hours for patients with growth of bacteria, indicating that a bladder incubation time of four hours can be hard to achieve due to the characteristic symptoms of a UTI.

In our study bacterial growth was found in 80% of the urine samples from women with UTI symptoms in PHC (Paper II) and growth of *E.coli* was identified in 72% of positive cultures, which is in-line with other studies that report that *E.coli* causes the majority of infections among outpatients regardless of age group.

Adherence to guidelines

Guidelines, adherence and risks

National guidelines for the treatment of UTI are published and updated on a regular basis. The most recent guidelines were published in 2017. The work with the guidelines is done via workshops and meetings with experts in the field, including representatives from in-and outpatient care. The work is led by the Medical Products Agency in Sweden in cooperation with the Public Health Agency of Sweden.

According to data based on all prescriptions from out-patient care in Sweden [106, 107], the use of the two first-line antibiotics (pivmecillinam and nitrofurantoin) has increased and the use of fluoroquinolones and trimethoprim has decreased from 2008 to 2013. This is in-line with the national recommendations and in-line with the results from the PRIS study (Paper I). Resistance to nitrofurantoin remains stable (1.1% for *E.coli* isolates from urine in 2010 and 1.2% in 2019) while resistance to mecillinam in *E.coli* has increased from 4.2% in 2010 to 4.8% in 2019 [13]. The increase in resistance is not a reason to change recommendations. Narrow spectrum antibiotics such as nitrofurantoin and pivmecillinam cause minimal damage to gut microbiota and contribute less to the selection of drug resistant bacteria than other antibiotic options [3, 77]. In men, fluoroquinolones are still prescribed to the majority of patients with uncomplicated UTIs even though the prescription rate of broad-spectrum antibiotics to men is decreasing. The continued high prescription rates for fluoroquinolones to men could be due to the change in recommendations for prescribing of UTI antibiotics in men that were first published in 2017, but probably also due to the more complicated anatomy of the male urinary tract and the concern of treatment failure with narrow-spectrum antibiotics in male UTI. In fact, the new treatment recommendations for men were based on limited evidence since there is a lack of studies on UTI in men. The increased ratio of narrow-spectrum antibiotics in the treatment of lower UTI is one step in the work towards better antibiotic prescribing to prevent the development of antibiotic resistance. While working towards this goal we need to consider the risk of under-treatment or withholding of proper antibiotic regime to specific patient groups. A clinical study of men with lower UTI is hard to perform in a Swedish context since the incidence is low. In Paper IV we describe that the incidence of complications within one month after a lower UTI in men was low-and there was no difference in outcome regarding complications between narrow- or broad-spectrum antibiotic treatment.

Reconsultations due to therapy failure and recurrence were more frequent in patients treated with narrow-spectrum antibiotics and trimethoprim, indicating that lower UTIs in men need specific considerations regarding safety net and follow- up after the initial antibiotic treatment with narrow-spectrum antibiotics. In-line with our study, a higher incidence of reconsultations due to treatment failure was observed in a study including 22 629 English men aged 18-64 with UTI, treated with nitrofurantoin and trimethoprim as compared to ciprofloxacin [108]. In a study including 129 Swedish men, recurrence within three months was more frequent with narrow-spectrum antibiotics as compared to trimethoprim [73] and in a Norwegian study the antibiotic switch rate within 14 days was more common in men treated with recommended antibiotics (pivmecillinam, nitrofurantoin and trimethoprim) as compared to fluoroquinolones and cefalexin [74].

A urine sample should always be obtained and sent for culture before treating UTI in men. The low rate of urine cultures performed in men in Paper IV is an important finding and a vital issue to address in the future work towards better adherence to guidelines.

In women with UTI several studies show that complications such as pyelonephritis or sepsis due to UTI are uncommon, 0.5-2.6% [36, 37] and a wide range of prescribing practices exists in different countries. Treatment recommendations with narrow-spectrum antibiotics for women is internationally considered as an appropriate choice due to minimal resistance and propensity for collateral damage and efficacy [109].

Antimicrobial resistance and treatment

Antibiotic resistance in *E.coli*

According to clinical guidelines for the treatment of UTI in non-pregnant women, there is no need for urine bacterial analysis before onset of empiric antibiotic treatment, the diagnose is based on the symptoms frequency, dysuria and urgency. Indications for urine culture in women are therapy failure, relapse, complicated UTI or relation to hospitalisation or other known risks of antibiotic resistance. This means that the knowledge about antibiotic resistance among women with uncomplicated UTI in primary health care is low since urine cultures are not analysed as a routine. In Sweden, antibiotic resistance surveillance is performed by Svebar (administered by Public Health Sweden). This database collects daily information on all clinical isolates from 20 of Sweden's clinical microbiological laboratories. Patient identification is not permitted in the system; thus, it is not possible to deduplicate findings. Duplicate findings will be reported, and it is not possible to separate urine cultures from primary care from cultures from hospital care [13]. In Paper II, we could compare all cultures from women attending primary

care with symptoms indicating an uncomplicated UTI in the study with culture results from the local clinical microbiology laboratory for women in the same age during the same time-period. The findings show differences regarding antibiotic resistance rates for ciprofloxacin, which could be due to a selected sample of more complicated infections in cultures from hospitals and primary care. To correctly be able to describe antibiotic resistance rates from PHC we need laboratories to be able to separate hospital data from PHC data.

We found an association between antibiotic treatment the last year and antibiotic resistance in *E.coli*, also described by others [18]. Even though we cannot draw any causal conclusions from this observed association, it is important to consider the development of antibiotic resistance as an adverse effect when antibiotic treatment is initiated. An association between travel abroad and antibiotic resistance in *E.coli* was observed in our study and has earlier been described in several studies [110-113]. This emphasises the relevance of a thorough patient history prior to antibiotic treatment, especially in cases with treatment failure.

Bacterial findings and antibiotic resistance rates differ between women and men [7, 13]. In Paper IV we could retrieve data on bacterial findings but not on antibiotic resistance. This was because of technical issues concerning the format of the data from the susceptibility testing. This is a limitation to the study since resistance pattern could affect the choice of treatment and the following risk for therapy failure, recurrence and complications. We found that only 55% of the patients diagnosed with an uncomplicated UTI had a urine sample analysed, which is not adherent to guidelines and could affect the treatment outcome since antibiotic resistance is known to be more frequent in UTI in men than in women.

Antibiotic prescribing

In total 80% of detected *E.coli* were susceptible to all tested antimicrobials and resistance rates to ciprofloxacin were lower compared to other PHC studies on antibiotic resistance in *E.coli* (Paper II) [114-117]. This could be due to lower antibiotic pressure in Sweden than in many European countries as antibiotic consumption is related to the development of AMR at both the individual and community level. The proportion of patients with UTI, which are prescribed UTI antibiotics, differ between the European countries and has been described to be between 56 and 99% [98]. The prescribing rates of antibiotics for UTIs may be influenced by many different factors other than the prevalence of *E.coli* in urine cultures. Some of these factors could be differences in national treatment guidelines and differences in GP's adherence to existing guidelines. Other factors sometimes discussed are uncertainty in diagnostic testing, differences in health care systems, availability to care and doctors' appointments. In Paper II we describe that 74% of the women were prescribed antibiotics empirically and that the uncertainty in diagnostic testing probably led to both over and under prescribing since 49% of patients with no significant growth of bacteria in urine were treated with antibiotics

while 14% of patients with bacterial growth in urine were not treated with antibiotics. Better diagnostic tools are needed to help target antibiotic prescriptions. Delayed prescriptions to selected patents is another method discussed to reduce antibiotic prescribing [82, 83].

In Paper III the median symptom duration after consultation among all patients prescribed antibiotics was four days, independent of bacterial growth in the urine sample. Patients not treated with antibiotics had symptom duration for a median of 6.5 days. The groups are unequal in size since most patients were treated with antibiotics. Nevertheless, the difference is interesting and could, in addition to a true effect of antibiotic treatment, be explained by methodological issues such as short bladder incubation time, the placebo effect or other effects of antibiotics regarding UTI symptoms that we are not aware of.

Symptoms and self-care

Many patients with UTI symptoms self-medicate prior to seeking care. A total of 63% of women with UTI symptoms described that they had tried to relieve symptoms in different ways. Cranberry products and plenty of liquids were the most popular self-medications (Paper III). Cranberry products are marketed by pharmacies to prevent and treat UTI. So far there is no RCT concerning treatment of acute uncomplicated UTI, while studies done on cranberry products to prevent UTI suggest that these can be an effective nutrition based non-antibiotic approach to prevent UTI recurrence among generally healthy women [85]. Women with UTI are often counselled to increase the intake of fluids. The belief is that liquids dilute and flush the urine and the bacteria. There are few studies in the area, data from one RCT showed reduced risks for recurrent UTI with increased water intake [91]. Painkillers including Ibuprofen (NSAID) were consumed by 10% of patients that had tried to relieve symptoms prior to visit (Paper III). NSAIDs have been studied in different clinical trials as an alternative option to antibiotics and been found to be, inferior to antibiotic therapy and might increase the risk of pyelonephritis [86, 87]. Uva-ursi has also been studied and no evidence of differences between Uva-ursi versus placebo or ibuprofen after 2-4 days has been shown [89], and further studies in the field are ongoing [118]. Antimicrobial-sparing approaches could be beneficial to avoid the antibiotic pressure, at least for women to start with, though antibiotics are still the most effective treatment for UTI and no study has so far shown evidence that antibiotics can be replaced by non-antibiotic options [119].

UTI in men- special considerations

Contact rates in PHC due to UTI were 232/1000 women and 37/1000 men in the Netherlands in the year 2014 [23]. Data from the PRIS record (Paper I) show that visits related to lower UTI were six times more common in women than in men, in-line with data from the Netherlands. The incidence of UTI increases in older men, most cases of UTI in men are found in men older than 60 years [25]. Older men are

more fragile, and comorbidities are more common. This could contribute to higher rates of prescribing of broad spectrum antibiotics to men. Irritative symptoms such as lower urinary tract symptoms (LUTS) are more common in older men as well as ABU, which makes it difficult to correctly diagnose a UTI and most patients with LUTS that contact PHC will be treated with antibiotics. This could affect the incidence of the outcome complications (Paper IV) as patients diagnosed with a UTI may in fact only have irritative symptoms and not a UTI and the actual incidence of UTI in men might be even lower than identified. On the other hand, this type of error would be hard to adjust for also in an RCT but we would be able to control for individual anamnestic factors. In our study, we included men aged 18-79 years, thus the oldest men were not included nor were prescriptions from multidose drug dispensing (a system of administration of medications) often used for patients living in nursing homes. A chronic infection in the prostate gland can result in treatment failure and recurrence after a UTI. It is not known how often the prostate gland is infected when a man has a lower UTI. Previously, broad-spectrum antibiotics were the only choice used to treat lower UTI in men, the reason was the good penetration to the prostate gland. Several studies show that treatment with broad-spectrum antibiotics increase the risk for infections with resistant bacteria 3-6 months after treatment [77, 120-122]. Treatment with fluoroquinolones can be associated with side-effects, and in 2018 the European Medicines Agency (EMA) recommended restricting the use following a review of disabling and potentially long-lasting side effects [70].

In our study there was no difference in serious complications such as pyelonephritis and sepsis between men treated with narrow-or broad spectrum antibiotics, thus narrow-spectrum antibiotics seem to be a proper first choice antibiotic in male UTI. Since reconsultations due to treatment failure and recurrence were more common in the group of men treated with narrow-spectrum antibiotics and trimethoprim, as compared with ciprofloxacin, it is important to have a "safety net" to inform patients to contact in case of persisting symptoms or recurrence or even better, to schedule a follow-up contact with the GP. In case of therapy failure, the antibiotic choice should be reconsidered.

Primary care clinical context

Uncomplicated UTIs are one of the most common infections in primary care. However, there are few Swedish studies describing symptoms, bacteriological aetiology, antibiotic resistance and antibiotic treatment in this group of patients. Studies in different European countries have been performed but since the health care systems, antibiotic treatment recommendations and patient populations differ between countries, the studies are not representative for the Swedish PHC population. The prospective observational studies (Paper II and III) have a

pragmatic design in order to describe uncomplicated UTI in the clinical setting. This was done to maximise applicability and generalisability. The intention was to follow the patient in "real life" and a wide spectrum of patient-centred outcomes were measured. The intention with this pragmatic design was to get a true description of symptoms and outcome in a group of patients that are very common in PHC. Women with uncomplicated UTI suffer from disturbing symptoms for several days. To be able to improve the management of this group of patients we need to do further studies concerning risk factors and treatment options in the PHC setting where the women will attend and where new research will be implemented.

Clinical studies performed in PHC are important, findings generated by clinical research must also be translated into effective treatments for patients who are seen in non-research settings.

Future research

To improve antibiotic prescribing and the adherence to treatment guidelines we need to continue the work with monitoring diagnosis linked prescribing. The PRIS register is now closed but hopefully new methods for diagnosis- linked antibiotic prescribing will make it easy for all prescribers in PHC to identify the local prescribing pattern to be able to improve the prescribing when needed.

Better and standardised national systems for electronic medical records would increase the possibility to follow changes in consultation rates due to infections and AMR related to antibiotic prescribing. Data from five counties revealed considerable differences in data structure, formats etc.

Future research needs to aim at better diagnostic methods to make empirical antibiotic prescribing more adequate. Patient-near tests with higher sensitivity and specificity than our existing urine dip-stick tests are needed. A quick result to identify relevant bacteria and susceptibility patterns would contribute to a safer antibiotic treatment in UTI. In men, there is a lack of studies regarding proper antibiotic choice and treatment duration for lower UTIs. So far, treatment recommendations are based on studies performed on women. Data from register based studies suggest that repeat prescriptions to men due to treatment failure and recurrence are more common in men when treated with narrow spectrum antibiotics but so far there is a lack of RCTs in this area. We need to find out more about the safety and efficacy of treatment with narrow-spectrum antibiotics in male UTI. Prospective studies are needed to investigate which antibiotic should be recommended and optimal duration of treatment in men. Studies would also benefit from a specific focus on the effect of antibiotic treatment to different age-groups. There is also a need for epidemiological studies on antibiotic resistance in urine

samples from men with lower UTI. To be able to perform larger studies on UTI in men, collaborations between several regions or countries are needed.

Women with UTI report a number of symptoms, some of which cause restricted activities and sick leave. Many women have prolonged symptoms in spite of negative urine cultures. Further studies will need to explore the best way of helping this patient group with better treatment options than antibiotics. Further studies should focus on exploring concerns and expectations in this group of patients. Women use a lot of expensive self-medication products; further research is needed to evaluate the effect on UTI symptoms. Self-medication products could be used as an antibiotic-sparing alternative if evidence shows that they help relieve symptoms without harm.

As the health care seeking pattern in primary health care changes with different care providers and new options for digital contacts and antibiotic prescribing, we need to continue to follow antibiotic prescribing and the development of AMR. We need to find new designs for future studies where we can benefit from the new techniques. Future studies also need to focus on education and antimicrobial stewardship. We need to be aware of the risk of inappropriate antibiotic prescribing when physical consultations become less common and care providers get more heterogeneous and will get harder to reach for education and monitoring in questions regarding antimicrobial stewardship.

Svensk sammanfattning

Urinvägsinfektioner (UVI) är en av de vanligaste orsakerna till antibiotika-förskrivning i primärvården. Hälften av alla kvinnor får någon gång i livet antibiotika för urinvägsinfektion. Samhällets höga antibiotikatryck medför en ökad risk för utveckling av resistenta bakterier och på sikt medför detta en risk för att tidigare lättbehandlade infektioner inte längre går att behandla med vanlig antibiotika. Antibiotikaresistens är en prioriterad fråga enligt WHO och i Sverige har ett 20-tal myndigheter tagit fram en gemensam handlingsplan för arbetet mot minskad antibiotikaresistens. För att kunna förskriva antibiotika till rätt patienter och kunna välja rätt sorts antibiotika behövs kunskap om det aktuella resistensläget bland de bakterier som orsakar infektioner och vi behöver veta vilka behandlingar som är effektiva för att lindra symtom och förhindra komplikationer. Idag är kunskap om resistens i primärvården ofta baserad på rapporter från mikrobiologiska laboratorier utan data kring patientens sjukhistoria och symtom.

Delarbete I

För att kunna förbättra antibiotikaförskrivning behöver man studera för vilka diagnoser förskrivningen skett och förskrivningen behöver följas över tid. För att bättre kunna följa hur antibiotika förskrivs vid olika infektionsdiagnoser skapades primärvårdens infektionsdatabas (PRIS) år 2007 av Region Jönköping. I detta delarbete användes PRIS databasen för att följa antal konsultationer och antal antibiotikarecept vid nedre UVI och pyelonefrit bland kvinnor och män under åren 2008, 2010 och 2013. PRIS-databasen innehåller data avseende ca 700 000 patienter listade på 90 olika vårdcentraler i olika delar av Sverige. Studien visar att antalet besök för UVI ökade något mellan 2008 och 2013. Besök för UVI var ca sex gånger vanligare bland kvinnor jämfört med män. Följsamheten till behandlingsriktlinjer när det gällde val av antibiotika var god vid förskrivning till kvinnor. Till män förskrevs fortfarande en stor andel bredspektrumantibiotika år 2013. Sedan dess har behandlingsrekommendationerna vid nedre UVI bland män förändrats och numera rekommenderas i första hand samma sorts smalspektrumantibiotika som till kvinnor.

Delarbete II

Diagnostiken av UVI hos kvinnor grundar sig på kvinnornas symtom. Urinodling med resistensbestämning tas bara vid specifika indikationer som till exempel graviditet eller när kvinnan inte tillfrisknar på behandlingen. Därför finns begränsad kunskap om förekomsten av bakterieväxt och antibiotikaresistens i odlingar bland kvinnor med UVI i primärvården. I denna studie togs urinodlingar för art- och resistensbestämning på alla kvinnor som deltog. Kvinnorna fick även fylla i en symtomenkät där de bland annat angav symtom och uppgifter om tidigare urinvägsinfektioner och antibiotikabehandling. De behandlades som vanligt av sin läkare och fick även uppge om de förskrivits antibiotika i samband med besöket och vilken sort. 304 kvinnor från åtta olika skånska vårdcentraler deltog i studien. Medianåldern var 46 år. Det växte bakterier i 80% av odlingarna, *E.coli* bakterier var vanligast och fanns i 72% av de positiva odlingarna. Totalt 80% av *E.coli* stammarna var helt känsliga för all testad antibiotika, bland stammar med resistens var resistens mot trimetoprim vanligast. Det fanns ett samband mellan antibiotikabehandling det senaste året och resistenta *E.coli* stammar. Tre fjärdedelar av kvinnorna blev förskrivna antibiotika, pivmecillinam var vanligast.

Delarbete III

Många kvinnor som drabbas av UVI beskriver långdragna besvär och flera studier visar att kvinnor ofta måste avstå från aktiviteter och även stanna hemma från arbete eller skola på grund av besvärande symtom. De flesta kvinnor som söker vård för UVI symtom behandlas med antibiotika. I denna studie ville vi ta reda på hur länge patienterna hade symtom innan de söker vård, om de blev bra av behandlingen, hur länge symtomen varade efter besöket och om det fanns särskilda riskfaktorer som bidrog till längre symtomduration efter besöket. Vi ville också ta reda på hur länge kvinnorna väntade med att söka vård och om de själva försökte lindra besvären innan de sökte. Kvinnorna fyllde i en enkät i samband med besöket, de fick lämna prov för urinodling. Efter besöket fick de fylla i en symtomdagbok i maximalt 10 dagar. Kvinnorna hade symtom i genomsnitt fyra dagar innan de sökte vård. Två tredjedelar försökte lindra besvären med ”huskurer”, olika tranbärsprodukter var vanligast Tre fjärdedelar av kvinnorna beskrev begränsningar i sina dagliga aktiviteter på grund av symtom och 10% behövde stanna hemma från arbete eller skola. Äldre kvinnor hade mer långdragna symtom, antibiotika bidrog till snabbare förbättring.

Delarbete IV

UVI är inte lika vanligt bland män som bland kvinnor och det är sannolikt orsaken till att det finns mycket få studier avseende urinvägsinfektioner bland män. Tidigare har man behandlat män med nedre UVI med bredspektrumantibiotika, vanligtvis kinoloner och trimetoprim. Eftersom andelen bakterier som är resistenta mot dessa medel har ökat under senare tid och målet är att minska användningen av bredspektrumantibiotika för att minska resistensutveckling i samhället, har man ändrat riktlinjerna för behandling av manlig UVI. Numera rekommenderas i första hand samma antibiotika som till kvinnor. Det saknas dock studier som visar om antalet komplikationer efter en UVI skiljer sig mellan män som fått smal- respektive bredspektrumantibiotika. I denna registerstudie kunde vi med hjälp av journaldata från fem olika svenska regioner, jämföra antalet fall med behandlingssvikt, återfall och komplikationer mellan män som behandlats med smal-respektive bredspektrumantibiotika. 21 124 besök bland män mellan 18 och 79 år som hade fått diagnosen distal UVI under åren 2012–2015 inkluderades. Det var mycket ovanligt med komplikationer och andelen komplikationer skilde sig ej mellan de olika behandlingarna. Andel patienter med terapisvikt och återfall var vanligare bland patienter som fått smal- jämfört med patienter som fått bredspektrumantibiotika. Behandling med smalspektrumantibiotika i form av pivmecillinam och furadantin bedöms vara ett gott val för att förebygga komplikationer vid nedre urinvägsinfektion bland män 18–79 år.

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Appendices (1-4)

Appendix 1. Diagnostic codes. Paper I

List of codes used for diagnose of lower UTI and pyelonephritis. ICD-10 code system or the primary care version KSH 97P.

Lower urinary tract infection (LUTI)

Code ICD 10/ KSH 97P	Diagnose
N30P	Lower UTI
N309	Cystitis/Lower UTI
N390X	Lower UTI
N390	Lower UTI
N300	Acute cystitis/ Lower UTI
N30	Lower UTI
N301	Lower UTI
N3012	Lower UTI
N308	Lower UTI
O862	Lower UTI after delivery

Pyelonephritis

Code ICD 10/ KSH 97P	Diagnose
N12	pyelnoephritis
N12P	pyelnoephritis
N129	pyelnoephritis
N109	pyelnoephritis
N110	pyelnoephritis
N111	pyelnoephritis
N118	pyelnoephritis
N119	pyelnoephritis

Appendix 2. Questionnaire urinary tract infections in primary care. Paper II and III

Original questionnaire (Swedish)

1

Forskningsstudie, urinvägsinfektioner i primärvård

Plats för lab-etikett

Dagens datum : _____

Personnummer (10 siffror) : _____

Telefonnummer:_____

Ålder (hela år) : ____ ☐Kvinna ☐Man

1. **Hur många dagar har du haft de besvär från urinvägarna som du söker för idag?**

   ☐mindre än en dag (mindre än 24 timmar)

   ☐en dag (24-48 timmar)

   ☐ längre, nämligen_____dagar (ange antal dagar)

2. **Svider det när du kissar?**

   ☐nej ☐lite ☐ganska mycket ☐väldigt mycket

3. **Gör det ont när du kissar?**

   ☐nej ☐lite ☐ganska mycket ☐väldigt mycket

4. **Måste du kissa oftare än vanligt?**

   ☐nej ☐lite oftare ☐ mycket oftare ☐väldigt ofta

5. **Har du svårare än vanligt att hålla urinen, (svårigheter att hålla tätt)?**

   ☐nej ☐ibland ☐ganska ofta ☐väldigt ofta

6. **Känns det som om du behöver kissa även om du inte behöver?**

   ☐nej ☐ibland ☐ganska ofta ☐väldigt ofta

7. Har du blod i urinen?

☐ja ☐nej

8. Upplever du att din urin luktar onormalt (illa)?

☐ja ☐nej

9. Har du ont i magen?

☐ja ☐nej

10. Har du feber?

☐ja, mer än 38 grader ☐nej

11. Har du andra besvär från urinvägarna?

☐ja, nämligen_____ ☐nej

12. Är du gravid?

☐ja ☐nej

13. Ammar du?

☐ja ☐nej

14. Har du varit utomlands de senaste 6 månaderna?

☐ja, ange land_____ ☐nej

15. Hur många gånger har en läkare givit dig diagnosen urinvägsinfektion?

☐aldrig ☐en gång ☐2-5 gånger ☐fler än 5 gånger

16. Om du tidigare haft urinvägsinfektion, när hade du senast urinvägsinfektion?

Månad_____ År_____

17. Hur många urinvägsinfektioner som krävt antibiotikabehandling har du haft det senaste året?_____

18. Har du behandlats med antibiotika på grund av en urinvägsinfektion de senaste 4 veckorna?

☐Ja, vilken antibiotika_____ ☐Nej ☐Vet ej

19. Står du på antibiotika just nu? ☐Ja, vilken antibiotika_____ ☐Nej

20. Av vilken anledning står du på antibiotika?_____

21. Har du behandlats med antibiotika för någon annan infektion de senaste 4 veckorna?

☐Ja, vilken antibiotika_____ ☐Nej ☐Vet ej

22. Har du diabetes? ☐Ja ☐Nej

23. Har du en kronisk njursjukdom?

☐ja, vilken?_____ ☐nej

24. Har du vanligtvis svårt att hålla urinen (inkontinens)?

☐Ja ☐Nej ☐Vet ej

25. Hur mycket begränsar dina urinvägsbesvär dig i dina dagliga aktiviteter (tex att orka motionera, gå och handla, träffa bekanta, sköta hushållet)?

☐inte alls ☐lite ☐ganska mycket ☐mycket

26. Har du varit tvungen att stanna hemma från arbete/skola på grund av dina urinvägsbesvär?

☐nej ☐ja_____dagar(ange antal dagar) ☐saknar arbete/skola

27. Blev du förskriven antibiotika vid dagens läkarbesök?

☐Ja ☐Nej

28. Om ja, vilket preparat?_____ ☐Vet ej

29. Ungefär hur lång tid hade urinen stått i blåsan när du lämnade dagens urinprov?

_____timmar_____minuter

30. Har du själv försökt lindra dina besvär med något läkemedel eller ”huskur” innan du sökte vård? ☐Ja ☐Nej

Hur har du i så fall behandlat?_____

Under dagens besök kommer du få lämna ett urinprov på vårdcentralens laboratorium även om din behandlande läkare inte ordinerat det. Vänligen lämna det ifyllda frågeformuläret till din läkare eller på laboratoriet.

Stort tack för din medverkan!

Questionnaire translated to English

Name

Date: _____

ID number: _____

Phone number:_____

Age:____ ☐Woman ☐Man

1. For how many days have you been experiencing your present urinary symptoms?

   ☐less than one day (less than 24 hours)

   ☐one day (24-48 hours)

   ☐longer, namely____days (state the number of days)

2. Do you feel a burning sensation when you urinate?

   ☐no ☐a little ☐rather much ☐very much

3. Is it painful when you urinate?

   ☐no ☐a little ☐quite much ☐very much

4. Do you have to urinate more often than usual?

   ☐no ☐a little more often ☐much more often ☐very often

5. Do you have moments when the urge to urinate is so strong that it is hard to control it?

   ☐no ☐sometimes ☐quite often ☐very often

6. Does it feel that you need to urinate even if you don't have to?

   ☐no ☐sometimes ☐quite often ☐very often

7. Is there blood in your urine?

   ☐yes ☐no

8. Does your urine have a bad smell?

   ☐yes ☐no

9. Do you have pain in your stomach?

☐yes ☐no

10. Do you have a fever?

☐yes, more than 38 degrees ☐no

11. Do you have other symptoms from the urinary tract?

☐yes namely_____ ☐no

12. Are you pregnant?

☐yes ☐no

13. Do you breast-feed?

☐yes ☐no

14. Have you been abroad the last 6 months?

☐yes, in what country? _____ ☐no

15. How often has a doctor diagnosed you with a urinary tract infection?

☐never ☐once ☐2-5 times ☐more than 5 times

16. If you have had urinary tract infections before, when was the last time you had a urinary tract infection?
Month_____Year_____

17. How many urinary tract infections treated with antibiotics did you have in the past year (last 12 months)?_____

18. Have you been treated with antibiotics due to urinary tract infection the last 4 weeks?

☐yes, namely_____ ☐no ☐I don't know

19. Are you taking antibiotics at the moment?

☐yes, what antibiotic?_____☐no

20. What is the reason (diagnosis) for the actual antibiotic treatment?_____

21. Have you been treated with antibiotics due to other reasons the past 4 weeks? ☐yes, what antibiotic?_____ ☐no ☐I don't know

22. Do you have diabetes?☐yes ☐no

23. Do you have a chronic kidney disease?

☐yes, what is the name of the disease?_____ ☐no

24. Do you usually have accidental urine loss (incontinence)?

☐yes ☐no ☐I don't know

25. How much do your urinary symptoms bother you in your daily activities (for example physical activities, shopping, social activities, do housework)?
☐not at all ☐a little ☐quite much ☐much

26. Did you have to stay home from work/school due to your urinary symptoms?

☐no ☐yes_____days (note number of days) ☐don't work or go to school

27. Were you prescribed antibiotics due to your urinary symptoms today?

☐yes ☐no

28. If yes, what antibiotic? _____ ☐I don't know

29. How much time passed between the urine sample you produced for testing today and the previous urination?

_____hours_____minutes

30. Did you try to ease symptoms with any "home remedies" before booking an appointment at the primary health care clinic? ☐yes ☐no

31. What kind of "home remedies" did you take?_____

During today's visit you will be asked to pass a urine sample at the laboratory even if your treating physician did not order it. Please submit the completed questionnaire to your doctor or at the laboratory.

Thanks for your participation

Appendix 3. Symptom diary. Paper III

Original diary (Swedish)

Personnummer_____

Symtomdagbok

För att vi ska få en bättre uppfattning om hur dina besvär från urinvägarna förändras efter läkarbesöket och hur mycket dina urinvägssymtom påverkar ditt dagliga liv är vi tacksamma om du vill fylla i symtomdagboken varje dag efter läkarbesöket. Vi är tacksamma om du fortsätter fylla i dagboken till och med en dag efter att du blivit symtomfri. Om du fortfarande har symtom efter 10 dagar behöver du inte fortsätta fylla i dagboken. Starta idag, den dag du sökte vårdcentralen. Detta är dag 1. Ge varje symtom en gradering från 0-5 varje dag, för vissa frågor finns endast svarsalternativen ja och nej i rutan. När du avslutat dagboken, vänligen returnera den i bifogat, frankerat kuvert. Skulle du inte bli bra på behandlingen och behöver uppsöka vård igen är vi tacksamma om du vill notera detta i symtomdagboken för aktuell dag.
Vi är tacksamma om du skickar in dagboken även om du inte lyckats fylla i den fullständigt.

Dag 1= samma dag som du sökt din vårdcentral för urinvägsbesvär

Poäng	*Besvärens svårighetsgrad*
0	*Normal/inga besvär*
1	*Nästan inga besvär*
2	*Lätta besvär*
3	*Måttligt svåra besvär*
4	*Svåra besvär*
5	*Mycket svåra besvär*

Personnummer_____

	Dag 1 Datum:	**Dag 2** Datum:	**Dag 3** Datum:	**Dag 4** Datum:	**Dag 5** Datum:	**Dag 6** Datum:	**Dag 7** Datum:	**Dag 8** Datum:	**Dag 9** Datum:	**Dag 10** Datum:
1. Svider det när du kissar?										
2. Gör det ont när du kissar?										
3. Kissar du oftare än vanligt?										
4. Medför dina urinvägssymtom besvär med att klara dina dagliga aktiviteter?										
5. Om du behövde gå upp för att kissa i natt, hur mycket besvärade det dig?										
6. Har du svårare än vanligt att hålla urinen? Ange även besvärens svårighetsgrad.	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja
7. Har du blod i urinen?	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja
8. Upplever du att din urin luktar mer illa än vanligt?	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja
9. Har du ont i magen?	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja
10. Har du feber?	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja
11. Har du stannat hemma från arbete/skola idag pga dina urinvägsbesvär?	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja	☐nej ☐ja
12. Här kan du ange övriga symtom.										

Poäng
0 = Normal/inga besvär
1 = Nästan inga besvär
2 = Lätta besvär
3 = Måttligt svåra besvär
4 = Svåra besvär
5 = Mycket svåra besvär

Symptom diary translated to English

To better understand how your urinary tract symptoms progress after the visit and how the symptoms affects your daily life, we would kindly ask you to fill out the diary every day after the visit. We would appreciate if you can continue until all symptoms are gone and after that fill out the diary one additional day. If you still have symptoms after 10 days, you don't need to continue with the diary. Start, the same day as the visit at the primary health care clinic (day 1). Grade each symptom from 0-5 for each day. For some questions you can only answer with yes and no. Once you have finished your diary, please return it in the enclosed envelope. Please note on the actual date in the diary if you don't feel better and you need to reconsult.

Please return the diary even if you were not able to answer all the questions.

Day 1= the same day as the visit at the primary health care clinic

Number	Grading of symptoms
0	Normal/no symptoms
1	Almost no symptoms
2	Slight symptoms
3	Moderately bad symptoms
4	Bad symptoms
5	Very bad symptoms

	Day 1 Date:	**Day 2** Date:	**Day 3** Date:	**Day 4** Date:	**Day 5** Date:	**Day 6** Date:	**Day 7** Date:	**Day 8** Date:	**Day 9** Date:	**Day 10** Date:
1. Do you have dysuria (a burning sensation when you urinate) ?										
2. Is it painful when you urinate?										
3. Do you have to urinate more often than usual?										
4. How much do your urinary symptoms bother you in your daily activities?										
5. If you had to get up from bed this night to urinate, how much did that bother you??										
6. Do you have urge to urinate?	☐no ☐yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes
7. Please note the grading of your urge.										
8. Is there blood in your urine?	☐no ☐yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes
9. Does your urine have a bad smell?	☐no ☐yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes
10. Do you have pain in your abdomen?	☐no ☐yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes
11. Do you have a fever?	☐no ☐yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes
12. Did you have to stay home from school/work today due to urinary symptoms?	☐no ☐yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes	☐ no ☐ yes
13. Here you can add other urinary symptoms.										

Appendix 4. Diagnostic codes. Paper IV

List of codes used for diagnose of lower UTI. ICD-10 code system or the primary care version KSH 97P.

N30-P
N30.-P
N300
N30.0
N308
N30.8
N309
N30.9
N390
N39.0
N39.0X
N390X

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Urinary tract infections in primary care

Helena Kornfält Isberg is a general practitioner working at Kärråkra primary health care center in Eslöv, Sweden. In this doctoral dissertation, antibiotic prescribing and antibiotic resistance in urinary tract infection, one of the most common infections treated with antibiotics in primary care, is studied. Symptoms in women seeking treatment with lower urinary tract infection in primary care are described as well as symptom duration. Differences in outcome in men with lower UTI treated with narrow or broad spectrum antibiotics are explored. The final goal of this research is better care and antibiotic prescribing to patients seeking treatment with symptoms indicating lower urinary tract infection in primary care.

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