

# General practitioners do not systematically adhere to regional recommendations on treatment of uncomplicated urinary tract infections

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## ABSTRACT

**INTRODUCTION:** Uncomplicated urinary tract infection (uUTI) is a common reason for seeing a GP. In Denmark, it is debated if sulfamethizole or pivmecillinam should be recommended for empirical treatment of uUTIs. We evaluated sulfamethizole and pivmecillinam use in the five Danish regions from 2007 to 2011 and explored if the choice of antibiotic in primary care was in accordance with the regional recommendations for uUTI.

**MATERIAL AND METHODS:** Regional drug use data on pivmecillinam and sulfamethizole from 2007 to 2011 were retrieved from the Registry of Medicinal Product Statistics. Regional recommendations from the same period were identified. We calculated differences in consumption based on defined daily doses per 1,000 inhabitants per day (DID) of pivmecillinam and sulfamethizole between the five regions, and intraregional developments.

**RESULTS:** Four regions had recommendations on uUTI in 2011. From 2007 to 2009, sulfamethizole was the only antibiotic recommended. Pivmecillinam was recommended along with sulfamethizole in one of four regions from 2010, which increased to two regions in 2011. During the five-year period, sulfamethizole consumption decreased in all regions. The absolute decrease ranged from 0.4 to 0.6 DID. Pivmecillinam consumption increased steadily; the absolute increase ranged from 1.5 to 2.5 DID. During the whole period, the total pivmecillinam consumption was higher than the total sulfamethizole consumption.

**CONCLUSION:** Pivmecillinam dominated the treatment of uUTIs, whereas sulfamethizole prevailed in the regional recommendations, which suggests a lack of adherence to regional recommendations.

**FUNDING:** not relevant.

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In Denmark, there has been debate about the most rational choice of antibiotic for the treatment of uUTI [3].

During many years, sulfamethizole has been used as the standard first-choice treatment, but due to the increasing resistance of *E. coli* to sulfamethizole [4], authors have recommended pivmecillinam as first-choice antibiotic [5]. A newly performed randomised controlled study comparing the effect of different antibiotics in patients with uUTI showed a faster relief of symptoms in patients treated with pivmecillinam than in patients treated with sulfamethizole. However, five days after initiation of treatment, there was no significant difference in either clinical or bacteriological cure between the two antibiotic regimes [6].

In 2007, five new Danish regions were established and the same year the first regional recommendations for antibiotic pharmacotherapy in primary care were published. Regional recommendations are formulated by regional pharmaceutical consultants on the basis of the National List of Recommended Drugs by the Institute of Rational Pharmacotherapy (IRF) and the recommendations are published online at [basislisten.dk](http://basislisten.dk) [7].

The aim of this study was to investigate prescription of sulfamethizole and pivmecillinam in the five Danish regions (2007-2011) and to analyse whether the choice of antibiotics for uUTI were in line with regional recommendations.

## MATERIAL AND METHODS

### Data source

Data on regional drug use of sulfamethizole and pivmecillinam in the five regions in Denmark (Region of the Capital, Region of Zealand, Region of South Denmark, Region of Central Jutland and Region of North Jutland) were obtained from the Registry of Medicinal Product Statistics (RMPS) [8]. The RMPS contains individual-level information on all redeemed prescription drugs bought at Danish community pharmacies. The information in the RMPS relevant for this study includes age, gender and region of residence, date of purchase, the anatomical therapeutic chemical (ATC) classification, and total defined daily doses per 1,000 inhabitants per day (DID).

## ORIGINAL ARTICLE

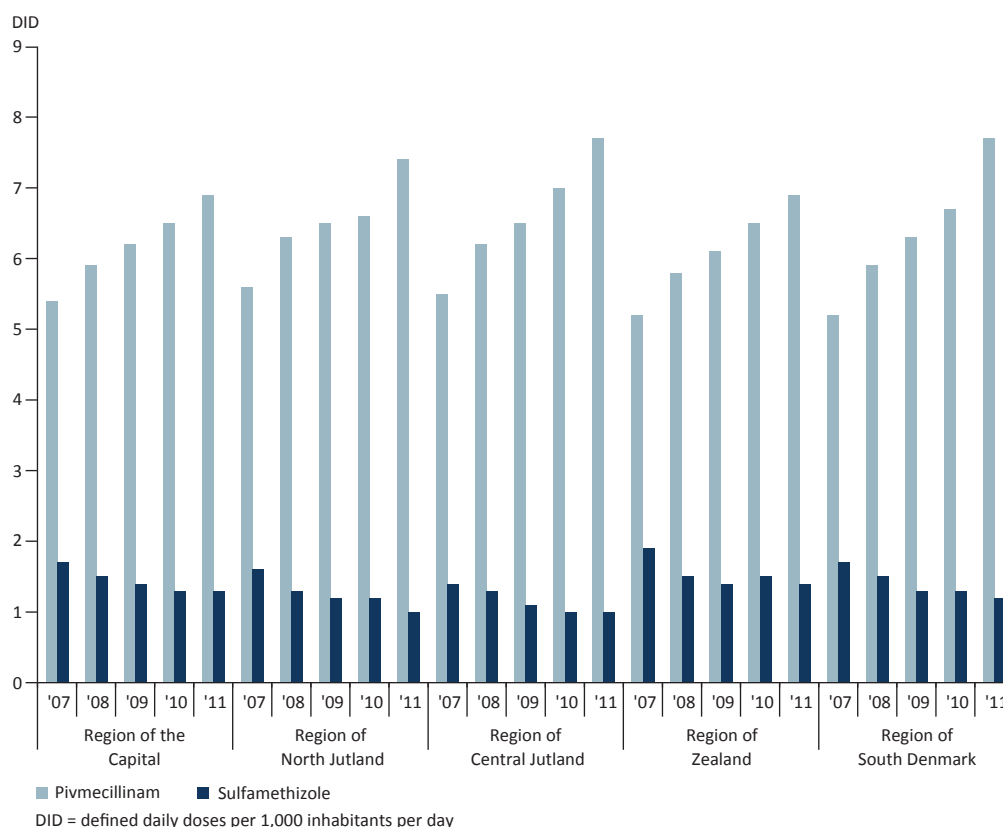
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Uncomplicated urinary tract infection (uUTI) is one of the most frequent reasons for seeing a GP. A total of 10-20% of all antibiotics in primary health care (PHC) are prescribed for treatment of UTIs [1]. uUTI is defined as a urinary tract infection in an adult non-pregnant and otherwise healthy woman with no anatomical abnormalities or presence of foreign bodies. Approximately 80% of uUTIs are due to *Escherichia coli* infections [2].

FIGURE 1

Prescription of pivmecillinam and sulfamethizole to women aged 15-64 years in the five Danish regions in 2007-2011.



Furthermore, data in the RMPS are organised by primary and secondary health care and are considered to have a unique completeness and validity [9].

#### Data selection

All prescriptions in the PHC of either sulfamethizole (ATC J01EB02) or pivmecillinam (ATC J01CA08) redeemed by women aged 15-64 years within the study period from 1 January 2007 to 31 December 2011 were included in the study.

#### Regional recommendations

The regional recommendations concerning antimicrobial drug treatment of uUTI in PHC that were in place from the beginning of 2007 to the end of 2011 were retrieved from the regional pharmaceutical consultants editing basislisten.dk.

#### Statistical methods

Descriptive statistics were used to analyse the data collected. Data were divided into five groups according to the Danish regions and presented by year. The drug use data on pivmecillinam and sulfamethizole, respectively,

were summarised within each regional group. The absolute and relative differences between the drug utilisations between and within each region were calculated.

*Trial registration:* not relevant.

## RESULTS

### Antibiotic drug use

**Figure 1** shows the use of sulfamethizole and pivmecillinam in the five Danish regions during the study period (2007-2011). Over the five-year period, the use of sulfamethizole decreased in all regions. The absolute decrease varied from 0.4 to 0.6 DID, on average 0.48 DID (a 29% reduction). During the entire period, the lowest use of sulfamethizole was seen in Region of Central Jutland. On the contrary, the use of pivmecillinam increased each year in all five Danish regions. The absolute increase was from 1.5 to 2.5 DID (36% on average) with the highest increase, 2.5 DID, found in Region of South Denmark.

### Regional recommendations

The regional recommendations on antibiotics for uUTI



TABLE 1

| Region          | 2007           | 2008           | 2009           | 2010                                                      | 2011                                                                          |
|-----------------|----------------|----------------|----------------|-----------------------------------------------------------|-------------------------------------------------------------------------------|
| Capital         | Sulfamethizole | Sulfamethizole | Sulfamethizole | Sulfamethizole                                            | Sulfamethizole<br>(Pivmecillinam) <sup>b</sup><br>(Trimethoprim) <sup>b</sup> |
| North Jutland   | Sulfamethizole | Sulfamethizole | Sulfamethizole | Sulfamethizole                                            | Sulfamethizole                                                                |
| Central Jutland | –              | –              | –              | –                                                         | –                                                                             |
| Zealand         | –              | –              | Sulfamethizole | Sulfamethizole                                            | Sulfamethizole                                                                |
| South Denmark   | –              | –              | Sulfamethizole | Sulfamethizole <sup>a</sup><br>Pivmecillinam <sup>a</sup> | Sulfamethizole<br>Pivmecillinam                                               |

Danish regional recommendations for antibiotic choice in the treatment of uncomplicated urinary tract infection in general practice in 2007-2011.

a) Published June 2010.

b) Data from “Antibiotic Prescribing Guidelines for Primary Care” at sundhed.dk (Region of the Capital) and not basislisten.dk. Published May 2011.

are presented in **Table 1**. Region of Central Jutland has never had a regional recommendation on antibiotics for UTIs, and the first regional recommendation for Region of South Denmark and Region of Zealand was published in 2009. Table 1 shows that in the majority of the Danish regions, sulfamethizole was the recommended antibiotic over the whole five-year period. This means that the choice of pivmecillinam for uUTI (Figure 1) was not in line with the regional recommendations. In 2010, Region of South Denmark introduced pivmecillinam to their regional recommendations on antibiotics for uUTI. Subsequently, in 2011, Region of the Capital published the “Antibiotic Prescribing Guidelines for Primary Care” which includes sulfamethizole, pivmecillinam and trimethoprim in the treatment guideline for uUTI.

## DISCUSSION

### Strengths and limitations of the study

A major strength of this study was the use of the RMPS as a data source. In Denmark, all prescription drugs are registered electronically, linked to the unique personal identification number (CPR number) and transferred automatically to the register. Consequently, the RMPS covers the entire nation and is assessed to contain highly valid and reliable data [9]. Furthermore, in Denmark, all antimicrobial agents are prescription medication only and thus redeemed prescriptions reflect the actual utilisation. In addition, sulfamethizole and pivmecillinam are used almost exclusively for treating UTIs and the prescription sales of sulfamethizole and pivmecillinam are therefore considered to reflect antibiotic treatment of uUTI [3]. Another study strength was the thorough identification of all valid regional recommendations. All current editors have examined their archives and identified all the applicable editions within the study period.

One potential limitation of this study may be the inclusion of antibiotic prescriptions to women with episodes of complicated UTIs (misclassification bias). The

age range of women (15-64 years) was, however, in accordance with several previous studies evaluating treatment of uUTI [3, 6, 10]. The potential episodes of complicated UTIs relevant to the study group include recurrent episodes of uUTIs within three months, UTIs among pregnant women and postmenopausal women. However, complicated UTIs constitute a limited number of all UTIs, and the majority of complicated UTIs occur in men, children, elderly women and inpatients [1, 2]. Prescription of pivmecillinam for other infections, i.e. salmonellosis [11], may constitute another potential misclassification bias. However, antibiotic treatment of salmonellosis is only recommended for severe infections occurring in infants, immunosuppressive patients and in geriatric patients. Hence, this potential misclassification bias is not believed to have had a substantial influence on the main results.

The drug use examined in the study was restricted to sulfamethizole and pivmecillinam. Other antibiotics may have been prescribed for uUTI, e.g. trimethoprim and nitrofurantoin. However, none of the mentioned drugs acted as part of the debate concerning uUTI treatment, and only one of them (trimethoprim) was included in one of the regional recommendations in 2011 (Region of the Capital). An additional analysis of the use of trimethoprim and nitrofurantoin showed only a minor use (0.6 DID and 0.9 DID on average, respectively) with little variation (< 0.1 DID) over the five-year study period and among the regions [8]. For this reason, trimethoprim and nitrofurantoin were not included in the study. Similarly, other recommendations than the regional ones have been available for the GP such as the recommendations from Danish Drug Information published online at pro.medicin.dk. Due to the regional focus of the study, all other recommendations were excluded.

Potentially, selection bias can have occurred as data from the RMPS are not standardised for variation in age between regions. However, data from StatBank Den-

Sulfamethizole has traditionally been used in the treatment of uncomplicated urinary tract infections.



mark show only slight differences in the proportion of women aged 15-64 years between the regions (range of proportion varied from 0.32 to 0.34) [12]. Thus, we do not believe that this potential bias had any substantial influence on our results.

### Discussion of the main results

In general, the use of pivmecillinam was increasing and dominated the actual treatment of uUTI, whereas sulfamethizole prevailed in the regional recommendations. This suggests a lack of adherence to regional recommendations. In 2007, sulfamethizole was recommended as first-choice antibiotic for uUTI in two out of five regions, and in 2011 this was the case in four of the five regions. In the same period, the use of sulfamethizole decreased with 0.48 DID on average (a 29% reduction), while the absolute increase in the use of pivmecillinam was from 1.5 to 2.5 DID (36% on average).

In Region of North Jutland, sulfamethizole was recommended as first-choice antibiotic for uUTI during the entire study period (2007-2011). Nevertheless, the use of sulfamethizole decreased continuously, while the use of pivmecillinam increased, notably within the five-year period. At the end of the study period, Region of North Jutland showed the lowest use of sulfamethizole (1.0 DID) and the second highest use of pivmecillinam (7.4 DID) among the regions. Thus, a mismatch between regional recommendation and drug use was seen in Region of North Jutland. On the other hand, the steep increase in the use of pivmecillinam from 6.7 DID in 2010 to 7.7 DID in 2011 (15%) in Region of South Denmark may reflect the introduction of pivmecillinam in the regional recommendations in 2010.

Several possible factors may explain the observed trends. Firstly, the GPs may not have been aware of the existence of regional recommendations. However, an evaluation of the organisation of pharmaceutical consultants in Region of the Capital showed that 98% of the GPs were aware of the regional recommendations [13]. Secondly, the same evaluation showed that 22% of the GPs do not use the regional recommendations despite

being aware of their existence. This possible lack of agreement may be due to experience of treatment failure (lack of outcome expectancy) [14]. Thirdly, the GPs may also have adhered to other recommendations, e.g. the national recommendations from IRF or the Danish Drug Information at [pro.medicin.dk](http://pro.medicin.dk). Since 2005, these recommendations have recommended pivmecillinam and sulfamethizole equally [15]. Finally, the debate in Danish journals concerning the increasing resistance rate in *E. coli* and the potential clinical consequences due to a reduced efficacy of sulfamethizole in the treatment of uUTI [5, 16] may have contributed to a shift in attitude towards the first-choice antibiotic (to uUTI), leaving pivmecillinam as the preferred choice [14].

Few studies have investigated the Danish GPs' attitude and behaviour regarding adherence to recommendations and guidelines. In a qualitative study, Carlsen & Kjellberg explored GPs' attitude towards clinical guidelines in Denmark and Norway and found that the GPs experienced difficulties in keeping updated on new guidelines and stressed that format, simplicity, accessibility and implementation strategy influence the use of guidelines [17]. Treweek et al found that the familiarity with clinical recommendations among Norwegian GPs was limited and that the adherence to national recommendations, particularly those published by their own scientific college, was higher than adherence to regional recommendations [18]. In a recent Norwegian prescription database study comparing redeemed prescriptions and national recommendations, Agdestein et al found that the choice of antibiotics conformed well to national recommendations in Vestfold, Norway [10].

Regarding the efficacy of treatment with sulfamethizole and pivmecillinam, studies have found no significant difference [3, 6, 16]. Several factors, though, speak in favour of treatment with pivmecillinam. Pivmecillinam, which is recommended as first treatment choice in Norway [10] and Sweden [19], was found to be superior to placebo in both bacteriological and clinical cure [20] and has a relatively low risk of antimicrobial resistance (6-9%) [4]. On the other hand, some studies indicate that sulfamethizole may have the same efficacy as pivmecillinam, despite the higher risk of antimicrobial resistance to *E. coli* found in the laboratory [6]. Furthermore, the resistance pattern of *E. coli* to sulfamethizole has been relatively stable during the past 10-15 years, whereas the resistance proportion of pivmecillinam has shown a slight increase within the past couple of years [4]. Both antibiotic drugs are generally well and equally tolerated, but minor adverse effects, such as nausea and diarrhoea, have been reported in up to 14% of the treated patients [6].

The present study suggests a further discussion concerning the antibiotic recommendations for uUTI.

Since several studies suggest that GPs only embrace and use a limited part of the multitude of clinical guidelines and recommendations available in general practice, it seems fair to ask if it is reasonable with five different Danish regional recommendations and several national recommendations on antibiotic treatment of uUTIs. The regional recommendations are all based on the national recommendations from the IRF, but with regional priorities regarding efficacy and price [7]. Probably, adherence to regional recommendations on antibiotic treatment of uUTIs will increase if they are unified with the national recommendations and a greater emphasis is placed on the evidence the recommendations are based on.

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