

Contribution of urinary tract infections to antibiotic consumption in Europe[†]

Thomas Kopf ^{1,*}, Jean-Marc Bohbot ², Heinz Kölbl ³, Annette Kuhn ⁴, Sławomir Poletajew ⁵ and Florian Wagenlehner ⁶

¹ MCM Klosterfrau Vertriebsgesellschaft mbH, Cologne, Germany, part of the Klosterfrau Healthcare Group; Thomas.Kopf@klosterfrau.de

² Genito-Urinary Medicine Department, Institute Fournier, Paris, France; jmbohbot@msn.com

³ University Clinic for Gynecology, Clinical Department of General Gynecology and Gynecological Oncology, Vienna, Austria; heinz.koelbl@meduniwien.ac.at

⁴ Consultant Urogynecologist Frauenklinik, Inselspital, and University of Bern, Bern, Switzerland; Annette.Kuhn@insel.ch

⁵ Second Department of Urology, Centre of Postgraduate Medical Education, Warsaw, Poland; slawomir.poletajew@cmkp.edu.pl

⁶ Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig University, Giessen, Germany; florian.wagenlehner@chiru.med.uni-giessen.de

* Correspondence: Thomas.Kopf@klosterfrau.de; Address: MCM Klosterfrau Vertriebsgesellschaft mbH Gereonsmuehlengasse 1-11, 50670 Cologne, Germany; Tel.: +49 221 1652 225

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Abstract:

Impact of rising antimicrobial resistance within the European Union compels reconsidering the primary treatment of urinary tract infections (UTIs) with antibiotics. We thus examined the scope of UTI-related antibiotic use within European outpatient care by determining the volume of UTI-specific prescriptions and the share of UTI-related among prescribed broad-spectrum antibiotics. Our findings indicate generally high consumption, with 652 million packages of broad-spectrum antibiotics and additional 30 million packages of UTI-specific antibiotics. Based on a conservative 9.1% average of UTI-related among broad-spectrum antibiotics, overall UTI-related prescriptions amount to 89.6 million. Effective alternative treatments will be relevant for future therapeutic strategies.

Keywords: antibiotics; prescription; urinary tract infections; Europe; outpatient; antimicrobial resistance; alternative treatments

1. Introduction

Antimicrobial resistance represents a partial or complete loss of susceptibility toward antimicrobial treatments such as antibiotics. Emerging and steady increase of resistant microbes poses a threat for the effective treatment of infectious diseases and has become a global public health concern [1-3]. Loss of treatment response is particularly relevant in light of limited therapeutic options for the treatment of infections and declining development of innovative antibiotics [4]. Infections with antimicrobial-resistant microorganisms carry a higher risk of complications or a poorer outcome [2, 3]. Impact of antibiotic resistance within the European Union (EU) is considerable, with estimated 33,000 yearly fatalities and 1.5 billion € yearly costs due to health care needs and productivity loss [5]. Despite focus this public health issue has gained and the available evidence-based guidance on antimicrobial stewardship, high levels of resistance persist in the EU/ European Economic Area (EEA) countries for several combinations of bacterial species and antimicrobial groups [6]. Furthermore, antimicrobial resistance varies across European countries, notably

correlating with the use of antimicrobial treatments [2, 6, 7]. Overall health burden of selected antibiotic-resistant infections in the EU/EEA countries has previously been estimated to correspond to the combined burden of HIV, influenza and tuberculosis [8]. Although the average consumption of antibiotics in the EU had slightly reduced, from 34% recorded in 2016 to 32% recorded in 2018, their use concomitantly increased in five countries, with the highest increase of 5% recorded for Denmark [9]. Urinary tract infections (UTIs) were one of the most cited reasons for antibiotic use with the same percentage share as the flu and superseded only by sore throat and bronchitis. In addition, it is estimated that around 60% of antibiotics prescribed by general practitioners in OECD countries are used inappropriately, further contributing to the development of treatment resistance [3].

UTIs are some of the most common bacterial infections, affecting 150 million people each year worldwide and representing a significant cause of morbidity in infant boys, older men, and females of all ages, with the female population being predominantly impacted [10, 11]. UTIs are primarily treated by antibiotics, as recommended by different national and international guidelines [12, 13]. Approximately 20-30% of women with UTI will experience recurrence, either through relapse or reinfection [14]. Such recurrent infections are also treated by antibiotics. Some guidelines have been expanded to include the use of non-antibiotic options such as D-mannose based products, immunostimulation and estrogen supplementation for the prophylaxis of recurrent UTIs [15, 16]. Although UTIs can be caused by various bacterial strains as well as certain fungi, the underlying pathogen is most frequently *Escherichia coli*, which shows varying resistance to different antibiotics used for the treatment of UTIs and has been described as increasingly developing multidrug resistance in Europe [7, 10, 17-19]. Apart from the burden of accompanying side effects, antibiotic use notably contributes to the development of treatment resistance [7, 14]. This issue affects not only the adult but also the pediatric patient population. Prevalence of resistance to commonly prescribed antibiotics in primary care in children with UTIs caused by *E. coli* is high, as illustrated by the pooled resistance prevalence of 53.4% for ampicillin in countries within the Organization for Economic Co-operation and Development (OECD) [20].

Uropathogens are known to rapidly acquire antibiotic resistance and, given the right conditions, this resistance can rapidly spread to other bacterial species [21]. Reducing the consumption of antibiotics and curbing any avoidable, inappropriate, or unwarranted use in various patient populations is therefore vital, particularly in the treatment of UTIs [18]. Easy-to-use alternatives with a comparatively smaller burden of rather mild side effects are available for the prophylaxis and treatment of UTIs [2, 14, 21, 22]. Among the most studied nonantibiotic management options for recurrent UTIs are cranberries, probiotics, D-mannose, estrogens and immunostimulants [11]. Certain alternatives, such as D-mannose, also show good prospects for possible use in the treatment of acute UTIs [23]. Reconsidering the current use of antibiotics and alternative treatments for UTIs is an important step in tackling antimicrobial resistance. Our novel insights regarding the prescription of broad-spectrum and UTI-specific antibiotics in Europe illuminate the urgency of this issue.

2. Methods

Data on the prescription of broad-spectrum antibiotics as well as those specific to the treatment of UTIs within European outpatient care (excluding the UK) were obtained from IQVIA MIDAS 2019 [24]. UTI-related share among broad-spectrum antibiotic prescriptions in Germany and France was determined by matching their respective prescriptions with International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes [25, 26]. A conservative estimate regarding average UTI-related consumption of broad-spectrum antibiotics in Europe was achieved based on the assumption of prescription varying between the values established for Germany and France. Total number of UTI-related prescriptions was calculated by adding UTI-specific prescriptions to the average volume of UTI-related broad-spectrum antibiotics. Results were then used together with data from OECD [27] and Statista [28] to map per capita UTI-related to total antibiotic consumption, as well as the use of prescription vs. over-the-counter (OTC) antibiotics across Europe. Antibiotics were categorized based on the Anatomical Therapeutic Chemical (ATC) Classification [29].

3. Results and Discussion

In 2019, 652 million packages of broad-spectrum antibiotics were prescribed in the outpatient sector across Europe, and additional 30 million packages of so called “urinary anti-infectives” were prescribed specifically for the treatment of UTIs (Table 1). Overall antibiotic consumption thus amounted to estimated 1.5 packages per patient per year.

Table 1. General antibiotics and urinary anti-infectives considered in the presented index calculations.

| Antibiotics (ATC ¹ class, package volume determined) | Top 5 of all prescribed substances |
|---|------------------------------------|
| General Systemic Antibiotics (J1, 652 million) | Amoxicillin |
| | Amoxicillin/clavulanic acid |
| | Azithromycin |
| | Cefuroxime axetil |
| | Clindamycin |
| Urinary Anti-infectives (G4A, 30 million) | Fosfomycin |
| | Fosfomycin trometamol |
| | Furazidin |
| | Nitrofurantoin |
| | Nitroxoline |

¹ Anatomical Therapeutic Chemical (ATC) Classification.

UTI-related indications accounted for 13.1% of general antibiotic prescriptions in Germany, and 5.4% in France (Figure 1). Based on the ICD-10 classification, most broad-spectrum antibiotics were provided for UTIs without a specified site, followed by unspecified cystitis and acute cystitis, with a marginal share of other UTI-related ICD-10 codes. Assuming the share of UTI-related prescriptions among general antibiotics varies between the values determined for Germany and France, a conservative estimate results in a 9.1% average or 59.6 million packages of antibiotics. Adding the 30 million packages of UTI-specific antibiotics increases the overall number of UTI-related antibiotic prescriptions across Europe to an average of 89.6 million pack units, corresponding to 13.1% of the total number of antibiotic packages considered. Our estimates thus correlate well with the Eurobarometer report from 2018, in which 12% of respondents indicated antibiotic use for UTIs [9].

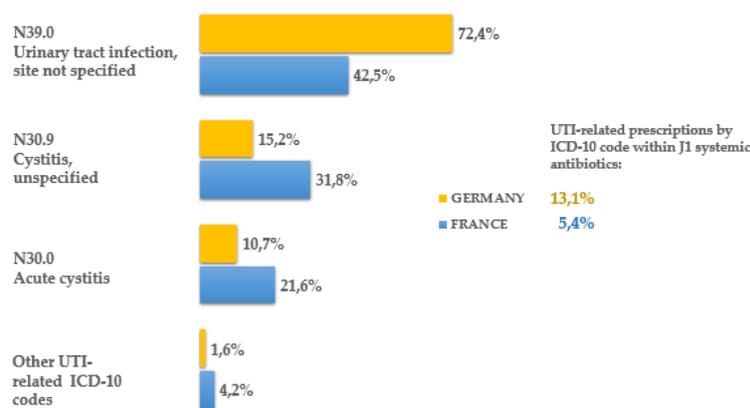


Figure 1. Common UTI-related indications for the prescription of general antibiotics in Germany and France based on ICD-10 classification. Share of UTI-related prescriptions among ATC J1 systemic antibiotics amounts to 13.1% in Germany and 5.4% in France.

Estimated per capita consumption of antibiotics within the female population varies across European countries, with a tendency towards higher consumption in countries located further south (Figure 2). Distribution pattern is partly similar to the findings of the previous Eurobarometer, which

reported highest use in Italy, and lowest in Sweden [9]. Notable is the apparent increase of antibiotic consumption in the Netherlands, which had been ranked among countries with lowest antibiotic consumption in the Eurobarometer. High consumption of antibiotics in France is attributable to high volume of prescriptions for urinary anti-infectives as well as prescriptions in indications other than UTI such as sore throat, common cold and bronchitis. Although Italy and Greece have previously been described as having the highest health burdens attributable to antibiotic-resistant infections among EU/EEA countries [8], our findings nevertheless suggest antibiotic consumption remains high in both countries.

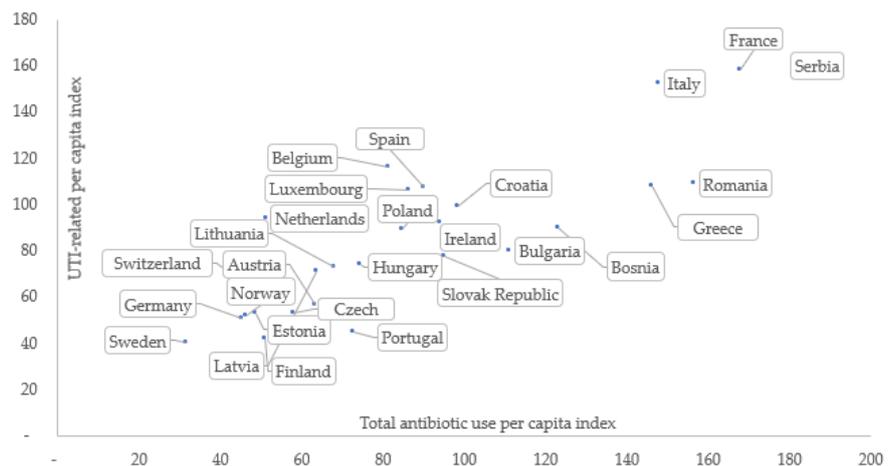


Figure 2. Per capita antibiotic consumption in female patients in European countries, with UTI-related per capita index (annual per capita pack unit consumption) determined based on an estimated contribution of 9.1% for ATC J1 antibiotics in addition to G4A antibiotics, and total antibiotic use per capita index calculated based on the overall prescription of J1 and G4A antibiotics.

Most patients in the EU reportedly obtain their antibiotics via a medical prescription [9]. Our data confirm that prescription-bound substances dominate with regard to antibiotic consumption and establish that this scenario applies to non-EU countries as well (Figure 3a). Poland is found to be an exception in light of its notable availability of OTC antibiotics (Figure 3b), which has previously been mentioned as a possible contributing factor regarding higher prevalence of resistance to nitrofurantoin, an antibiotic commonly used for the treatment of UTIs, compared to other European countries [30]. Limiting OTC availability of antibiotics has been suggested as part of a strategy to prevent overuse of antibiotics in the treatment of UTIs and overcome the challenges associated with increasing antibiotic resistance [18]. This approach might be useful in tackling the here reported considerable level of per capita antibiotic consumption in Poland.

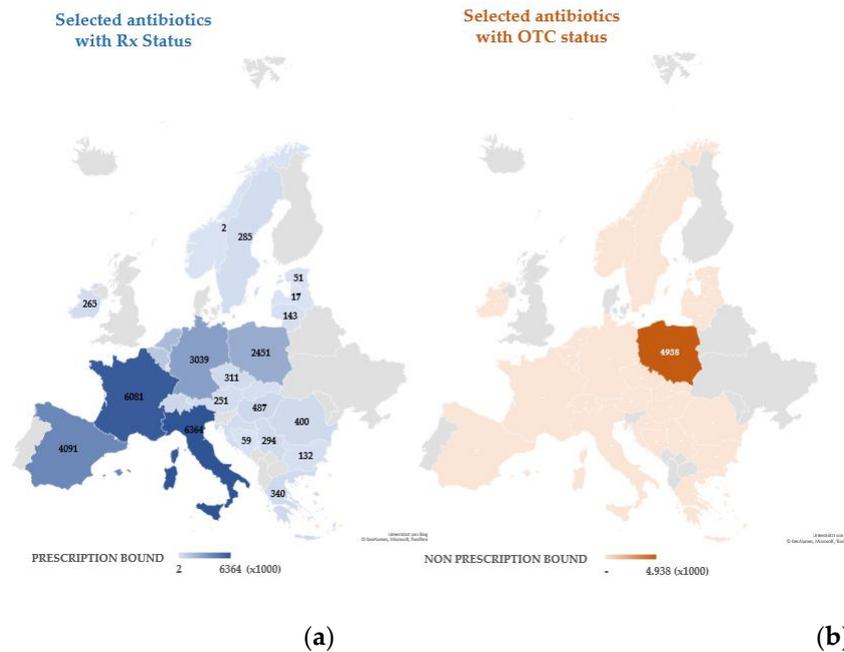


Figure 3. Consumption of antibiotics for urinary systemic conditions (ATC 12C1) and urinary anti-infectives (G41) across Europe, based on substance availability: (a) prescription antibiotics (Rx, blue); (b) over-the-counter (OTC) antibiotics (orange). Countries with available data are marked in the appropriate color.

4. Conclusions

Taken together, our findings indicate that antibiotic consumption in Europe is generally high and notably affected by UTI-related prescriptions. Varying consumption across Europe reflects heterogeneous indications and accordingly scope for significant reductions [6]. Use of antimicrobial treatments is strongly associated with development of resistance, and high levels of resistance persist in the EU/EEA countries for several bacterial species and antimicrobial groups [2, 6]. Effective alternative treatments such as D-mannose will therefore be of particular relevance for future therapeutic strategies. Most antibiotics are reportedly obtained from health care professionals (HCPs), who are also increasingly consulted on the value of non-antibiotic products, particularly by women with recurrent UTIs [9, 14]. Raising awareness on effective and safe alternatives with HCPs and patients will hence be an important step in reducing the consumption of antibiotics and thereby supporting the efforts of tackling antimicrobial resistance. Resistance is known to evolve rapidly, in contrast to its slow reversibility in clinical settings and at the community level [22]. Our findings therefore underline the need for urgent course change in the management of UTIs.

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