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Highlights

- Resistance to nitrofurantoin, fosfomycin and mecillinam was below 10% for *E. coli* isolates causing outpatient UTI in women indicating that these antibiotics are viable first line treatment options in all partner countries and that international treatment recommendations can be useful if no regional resistance data is available. However mecillinam and fosfomycin are only available for treatment in 50% of partner countries.
- Despite high levels of resistance to trimethoprim and trimethoprim/sulfamethoxazole these antibiotics are still recommended (without susceptibility testing) as first line in some partner countries.
- Over the counter sales of furazidin could explain the higher level of resistance to nitrofurantoin seen in Polish isolates.
- Patients from Russia had a significantly higher risk of having uncomplicated UTI caused by a resistant *E. coli* isolate (ciprofloxacin-resistant/ESBL-producing/Multi Drug Resistant) compared to patients from other partner countries.

Abstract

Objectives: In the Northern Dimension Antibiotic Resistance Study Finland, Germany, Latvia, Poland, Russia and Sweden investigated the resistance levels of *Escherichia coli* (*E. coli*) isolated from urine of outpatient women (18-65 years) that had symptoms of uncomplicated UTI by collecting samples in each respective nation.

Methods: In total 775 *E. coli* isolates from 1278 clinical urinary samples were collected from October 2015 – January 2017. Susceptibility testing was performed and results were interpreted according to the EUCAST criteria.

Results: Overall antibiotic resistance (ABR) rates to certain commonly used antibiotics, such as nitrofurantoin, fosfomycin and mecillinam were 1.2%, 1.3% and 4.1% (except for Germany that was missing result for mecillinam). Highest overall resistance rates were determined for ampicillin – 39.6%, trimethoprim -23.8%, trimethoprim/sulfamethoxazole -22.4%, amoxillin/clavulanic acid – 16.7% and ciprofloxacin – 15.1%, varying significantly among the countries. ESBL-production level was 8.7%. None of the isolates showed resistance to meropenem.

Conclusions: In most cases, low ABR rates were detected against the first line antibiotics recommended in national UTI treatment guidelines which give support to their future use. Our results also support the European Association of Urology guidelines stating that nitrofurantoin, fosfomycin and mecillinam are viable treatment options for uncomplicated UTI.

Keywords

Outpatient UTI, *Escherichia coli*, antibiotic resistance, risk factors, treatment recommendations, Western and Eastern Europe

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1. Introduction

Community-acquired uncomplicated lower urinary tract infection (UTI) in women is one of the most common reasons for prescription of antibiotics worldwide. Around 70-80% of uncomplicated UTIs are caused by *Escherichia coli* (*E. coli) [1-3]*.

In many countries, the practice is to start empirical antibiotic treatment without urine culture and antibiotic susceptibility testing (AST). Recommendations for empirical treatment are often based on antibiotic susceptibility test results of samples taken from complicated UTI caused by *E. coli*. However, patients with complicated UTI often possess risk factors such as higher age and previous antibiotic treatment and hospitalization periods. Thus, the pathogens isolated may show much higher levels of antibiotic resistance [3-5]. On the other hand there are also studies showing that the levels of Extended Spectrum Beta Lactamase (ESBL) colonisation in healthy carriers are increasing in the society [6, 7]. This trend is also seen in bloodstream infections in many European countries [8]. To avoid driving the development and spread of antibiotic resistance it is important to treat patients with narrow spectrum antibiotics that show good susceptibility in the local *E. coli* population. Some antibiotics like fluoroquinolones are also known to drive resistance, known as “collateral damage”, because many ESBL-producing *E. coli* are co-resistant to quinolones [9-11]. Reliable antibiotic susceptibility data on resistance levels of *E. coli* isolates causing uncomplicated UTIs is therefore critically needed.

We aimed to investigate the levels of antibiotic resistance in *E. coli* isolates causing UTI in female outpatients by collecting urine samples in primary care in Finland, Germany, Latvia, Poland, Russian Federation and Sweden (partner countries). To investigate risk factors associated with UTI caused by ESBL-producing, ciprofloxacin and/or multi-drug resistant (MDR) isolates we also collected data on age, antibiotic consumption during the last 12 months, hospitalisation during the last 6 months and travel habits. Data on current national/international treatment recommendations in each partner country were also reviewed in comparison to the resistance levels detected.

2. Methods and Material

2.1. Study set-up

Clinical study protocols for recruitment and collection of UTI samples and questionnaires were developed by all partner countries together. Ethical permission was obtained by each partner locally. Written consent was collected from each patient.

Women of age 18-65 years (including pregnant women) that had at least two of the specified symptoms: dysuria, frequent urgency and/or increased urinary frequency but in absence of vaginal symptoms (such as abnormal discharge, itching and/or inflammation of the vulva), fever and flank pain were included in the study. Exclusion criteria were intake of any kind of antibiotics for any

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indication during the last three months before the date of enrolment in the study. An exception from this was Germany that excluded only patients that had taken antibiotics the last two weeks as well as Poland and Finland that included some patients that had taken antibiotics the last three months. Different types of primary care centres (individual General Practitioners (GPs) or centres with several GPs) in the respective partner countries recruited and collected UTI samples from patients between October 2015 and January 2017. Each country sampled from the following regions: Finland - the Turku region (2 sites), Latvia - the Riga region (15 sites), Germany from regions of Berlin, Schleswig-Holstein, Northrhine-Westphalia and Baden-Württemberg (58 sites), Poland from Silesian voivodeship (1 site), Russia from 6 geographically distant cities representing European and Asian part of Russia (12 sites) and Sweden from the Stockholm region (7 sites).

The German data was collected simultaneously and in combination with another study [12].

Patients filled in a questionnaire, translated to the national language(s), which included questions regarding age, antibiotic treatment during the last 12 months, hospitalization during the last 6 months and travelling abroad along with travel destination (Supplementary file S1).

Data on presence of national guidelines for treatment of uncomplicated UTI and the recommended antibiotics for first and second line treatment as well as the availability of the antibiotics tested in Northern Dimension Antibiotic Resistance Study (NoDARS) were collected from each participating country.

2.2. Laboratory analysis

The urine samples were cultured based on internationally accepted standards [13]. The midstream urine was collected and the cut-off value for a positive urine culture was $\geq 10^3$ CFU/mL for *E. coli* isolates [13]. AST followed the EUCAST methodology and breakpoints (http://www.eucast.org/ accessed on 2018-02-15). Resistance rates were defined as the percentage of non-susceptible (R+I) isolates to the antibiotic in question. ESBL phenotype was defined as resistant and/or intermediate towards cefotaxime and/or ceftazidime.

MDR was defined as resistance to three or more classes of antibiotics defined as follows: 1) Nitrofurantoin; 2) Ampicillin, Mecillinam; 3) Amoxicillin/clavulanic acid; 4) Cefotaxime, Ceftazidime, Cefuroxime; 5) Meropenem; 6) Trimethoprim, Trimethoprim/sulfamethoxazole; 7) Fosfomycin; 8) Ciprofloxacin; 9) Gentamicin [14].

2.3. Statistics

Univariate risk analyses were performed only for patients that had both contributed with a sample and a questionnaire and that were positive for *E. coli* UTI. Firths logistic regression model was used to calculate odd ratios and confidence intervals for the risk analyses. No multivariate analysis was performed. Risk analysis for having a UTI with specific resistance determinants were performed both from a within- and between-countries perspective. In the within-country analysis the risk factors (e.g.

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hospitalization vs. non –hospitalization) in each partner country were investigated. In the between-countries analysis the patient population from each country as well as sub-populations (divided based on age, antibiotic treatment and hospitalization) was compared with the same population/sub-population in all other partner countries combined. The between-countries analysis was made to investigate if some patient populations had a higher risk of having resistant isolates compared to other partner countries combined. All statistical analysis was performed in R statistical software (version 3.2.5).

3. Results

3.1. Sample collection

In total 1278 urinary samples from patients with symptoms of lower UTI were collected. This resulted in 21.6% negative cultures, 16.8% that were positive for other species of bacteria and 58.9 % (n=775 *E. coli*) isolates, which went through AST (Table 1, Figure S2). In total *E. coli* caused 75.1% of culture positive infection. A total of 725 questionnaires were available for analyses and of these 469 were from patients with isolated *E. coli* and therefore used in the risk analyses (Table 3-5). No questionnaires were obtained from Germany.

3.2. Descriptive statistics for patient populations

The median and mean age of the patients positive for *E. coli* UTI were similar between partner countries (Table 1). The percentage of patients that had taken antibiotics during the last 12 months ranged from 21% (Latvia) to 55% (Poland). Moreover, in Poland 39% (n=37) and in Finland 17%, (n=5) of patients had taken antibiotics during the last 3 months. For the Polish patients also 12 % (n=11) were on antibiotics at the moment of enrolment in the study. Hospitalization during the last 6 months varied between partner countries in the range of 2% (Sweden) and 35% (Russia). Data on travel during the last 6 months is presented descriptively due to low numbers of travellers. Travelling abroad varied between partner countries from 15% (Poland) to 57 % (Finland) with the most common destination of Eastern and Mediterranean Europe (Table 1).

3.3. Antibiotic resistance of E. coli isolates

Table 2 shows resistance rates (R+I) of all 775 *E. coli* strains analysed. Nitrofurantoin and fosfomycin emerged as the most active drugs tested (1.2% and 1.3% resistance, respectively) followed by cefoxitin (3.1%) and mecillinam (4.1%). No resistance to meropenem among collected isolates of *E. coli* was detected. Highest rates of resistance were found for ampicillin (39.6%), trimethoprim (23.8%), trimethoprim/sulfamethoxazole (22.4%), and amoxicillin/clavulanic acid (16.7%). More than 15% of all *E. coli* showed resistance to ciprofloxacin. In total 13.9 % and 8.7 % of isolates had an MDR- and/or ESBL-phenotype, respectively (Table 2).

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Some AST profiles differed between partner countries. Comparatively high levels of resistance to nitrofurantoin and mecillinam (6.3% and 10.5%, respectively) and the highest resistance rates to trimethoprim (32.6%) and trimethoprim/sulfamethoxazole (31.6%) among the partner countries were observed in Poland. Almost two-fold higher rate of resistance to ciprofloxacin (28.4% vs. 15.1% for all countries) was detected in Russia. ESBL-production was also noticeably higher in Russia (15.7% vs. 7.7% for all countries). MDR varied in the range of 1.7% (Latvia) to 26.9% (Russia).

3.4. Risk analysis

Risk analysis for outpatient UTI caused by a ciprofloxacin resistant, ESBL-producing or an MDR *E. coli* was performed for different age groups, antibiotic treatment during the last 12 months and hospitalization during the last 6 months for both within and between partner countries (Tables 3-5). The reason for low representation of some phenotypes were a combination of low sample size as well as low resistance frequencies.

For all partner countries combined, significant risk factors of acquiring a ciprofloxacin resistant *E. coli* were the following: age of 51-65 years vs. age 18-30 years, previous antibiotic treatment during 12 months and previous hospitalization during 6 months (Table 3).

Within-country analysis showed significance only for certain countries for ciprofloxacin resistance: age of 51-65 years (Sweden), previous antibiotic treatment during 12 months (Poland) and previous hospitalization during 6 months (Russia) (Table 3).

Between-countries analysis of patient populations showed that the risk of having a ciprofloxacin resistant *E. coli* for outpatient UTI was significantly higher for patients in Poland and Russia and conversely lower for patients in Germany, compared to the patients in other partner countries (Table 3).

Between-countries analysis of sub-populations showed higher risk of ciprofloxacin resistance for Polish patients that previously received antibiotics during last 12 months and patients of the age group of 31-50 years. Russian patients of the age groups of 18-30 and 51-65 years also had higher risk of ciprofloxacin resistance compared with patients in the same age groups from other partner countries (Table 3). Between-countries analysis was also done for trimethoprim/sulfamethoxazole resistance (Table 2) which shows that patient population in Germany had a lower risk (OR: 0.6, 95% CI: 0.4 to 0.9) while Polish patients had a higher risk (OR: 1.9, 95% CI: 1.1 to 3.1) compared to other partner countries.

For all partner countries in total significant risk factors for having an ESBL-producing *E. coli* as cause of UTI were age of 31-65 years vs. age 18-30 years, previous antibiotic treatment during 12 months and previous hospitalization during last 6 months. Within-country analysis showed significance for ESBL-production for; age of 51-65 years, previous antibiotic treatment during last 12 months and previous hospitalization during 6 months only in Russia. Between-countries analysis showed that Russian patients had increased risk of having an ESBL-producing *E. coli* in outpatient UTI compared

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to patients in other partner countries, which was also confirmed by significantly higher risk in all sub-populations of Russian patients except for age group of 18-30 years (Table 4).
For all partner countries significant risk factors for having a MDR *E. coli* UTI were age of 51-65 years and previous antibiotic treatment during 12 months. Further within-country analysis showed significance for age of 51-65 years and previous hospitalization during 6-months for Russia only and previous antibiotic treatment during 12 months both for Russia and Poland. Between-countries analysis stated that the risk of MDR *E. coli* from outpatient UTI was significantly higher in Russian but significantly lower in German and Latvian patients compared to patients in other partner countries. Moreover, between-countries analysis of sub-populations and factors showed significantly lower risks of MDR *E. coli* for German patients both of the age groups of 31-50 and 51-65 years (Table 5).

3.5. Treatment recommendations

The structured survey of national treatment guidelines and availability of antibiotics showed that all partners had national UTI treatment guidelines except for Latvia (Table 6). The surveillance data, forming the basis of the guidelines, were to some extent based on data from complicated UTI studies. Poland had two (trimethoprim/sulfamethoxazole and trimethoprim) of five antibiotics recommended as first line which had a resistance level achieving 30% in our study. Otherwise the antibiotic resistance rates detected and compared to nationally recommend first line antibiotics indicate that they may be used for empirical treatment of acute uncomplicated UTI in outpatients. Some antibiotics (mecillinam and fosfomycin) were not available in all partner countries. Furthermore nitrofurantoin was not available in Poland but an analog - furazidin, was available over the counter instead (Table 6).

4. Discussion

NoDARS provides data on current susceptibility of uropathogen *E. coli*, causing outpatient UTI from 6 countries, namely Finland, Latvia, Germany, Poland, Russia and Sweden. The major strength of the NoDARS was the joint involvement of countries from both northern and eastern Europe with different antibiotic resistance situations, health-care system organization and antibiotic stewardship policies.

4.1. Resistance in all partner countries

NoDARS showed that resistance rates to nitrofurantoin, mecillinam and fosfomycin were low in all partner countries (below 10% for partner countries in total). This supports the guidelines from the European Association of Urology recommending fosfomycin, nitrofurantoin and mecillinam as first line treatment of uncomplicated UTI [4]. Studies of antibiotic resistance rates form the basis for decisions on empirical therapy options and they also provide input for formulating and updating local and national treatment or “best practise guidelines”.

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However, there are no universal upper threshold values of when a certain antibiotics becomes unsuitable for empirical use. For instance there are recommendations for use of specific antibiotics for empirical therapy of UTI only if the prevalence of resistance against it does not exceed 20% (for trimethoprim/sulfamethoxazole) or 10% (for fluoroquinolones) [15, 16]. Fluoroquinolone resistance rates above 10% were observed in all partner countries, except Latvia and Germany, indicating that it may not be a viable option for empirical use for community-acquired infection (Table 2), especially since it also a known driver of MDR [9-11]. Resistance to trimethoprim/sulfamethoxazole was around or above 20% in all partner countries (Table 2). Although there are studies supporting the use of trimethoprim/sulfamethoxazole as the first line treatment even in areas of 22% resistance rate this is likely not a suitable recommendation unless AST is performed, and should therefore be considered [17].

Collection of data on outpatient uncomplicated UTI that allows between-countries comparison on the AST of the causative microbe has previously been done in other settings [18, 19]. However, in NoDARS we further investigated risk factors and risk population which resulted in a finding that patients from Russia had a significantly higher risk of having outpatient UTI caused by a resistant *E. coli* (ciprofloxacin-resistant/ESBL-producing/MDR) compared to patients from other partner countries (Table 3-5).

Furthermore we investigated risk factors for acquiring a resistant pathogen within each country. Higher age (51-65 years), antibiotic treatment during the last 12 months and hospitalisation during the last 6 months were identified as risk factors in Russian patients of having a UTI with ESBL-producing and/or MDR *E. coli*. Poland had a higher risk of ciprofloxacin-resistant and MDR *E. coli* in patients that had taken antibiotics as well (Table 3-5).

4.2 Resistance country by country

In order to analyse our findings and how they correlate with/support currently available national guidelines we discuss results country by country below.

In **Finland,** the national UTI guidelines allow prescription of antibiotics to be made over the phone after a structured interview for a woman suffering for acute cystitis. Therefore difficulties were faced when recruiting of study subjects and this reflected in the number of samples collected. However, the AST resistance levels measured were in general below 20%, including the upper range of the confidence intervals, except for trimethoprim, trimethoprim/sulfamethoxazole, ampicillin and ciprofloxacin. The resistance levels were in line with data collected on urinary samples representing also complicated UTI and bacteremic *E.coli* isolates except that no ESBL-producing *E. coli* were detected in the NoDARS study [20]. Our results support the current Finnish national guidelines for uncomplicated UTI recommending nitrofurantoin or mecillinam as first line treatment. As the current national UTI guidelines are currently under review, the relatively high resistance rates for trimethoprim and trimethoprim/sulfamethoxazole can be taken into account during that process.

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For **Germany** resistance were below 20% for trimethoprim, trimethoprim/sulfamethoxazole and ciprofloxacin (upper range of the confidence intervals were slightly above 20%, Table 2). Resistance against ampicillin and, amoxicillin/clavulanic acid were above 30%. The results are in line with other studies which showed high resistance against ampicillin and amoxicillin and resistance below 20% against trimethoprimand ciprofloxacin [21]. The results support the current national guidelines for Germany recommending trimethoprim and nitrofurantoin as part of first line treatment for uncomplicated UTI.

In **Latvia** resistance rates were above 20% for trimethoprim, trimethoprim/sulfamethoxazole and ampicillin. In addition Latvia had very low rates of combination resistance and no ESBL-producing isolates were identified, which could be due to the sample size. Compared to Latvian data reported to GLASS on UTI the NoDARS resistance levels are slightly lower for ampicillin, cefotaxime, trimethoprim/sulfamethoxazole but the same for ciprofloxacin [22]. Another study, however small in size, indicated that for uncomplicated UTI in an outpatient setting nitrofurantoin or furazidin (nitrofurantoin analog) was mainly used [23]. All antibiotics are prescription only drugs in Latvia.

In **Poland** resistance rates were above 20% for trimethoprim, trimethoprim/sulfamethoxazole, ampicillin and ciprofloxacin. Mean age of patients in Poland as well as antibiotic consumption during the last 12 months was the highest among partner countries (Table 1). In conjunction with the fact Poland included patients that had taken antibiotics during the last three months this should be taken in to consideration when evaluating the external validity of the antibiotic resistance data for uncomplicated UTI in outpatients.

In Poland there is a complex situation for collecting outpatient UTI samples since furazidin is available over the counter and some patients have self-medicated before seeking healthcare. Nitrofurantoin use in the past or/and the easy availability of furazidin in the present may explain higher resistance to nitrofurantoin Poland (6%) compared to other partner countries (0 for all, except for Russia - 1%). High resistance of *E. coli* to nitrofurantoin (above 30%) has also been reported in another study on uncomplicated UTI in Poland [24]. In the same study, the resistance rate to ciprofloxacin (24.1%) was similar as reported in our study (25.3%). Our results suggest that trimethoprim, trimethoprim/sulfamethoxazole and ciprofloxacin included in the Polish treatment guidelines are unsuitable for empirical treatment.

For **Russia** resistance above 20% to ampicillin, trimethoprim, trimethoprim/sulfamethoxazole in combination with 15.7% for ESBL-producing *E. coli* correlate with the general situation in Russia according to the national surveillance program [25, 26]. Russia had the highest resistance rate to ciprofloxacin (28.4%) among partner countries which significantly limits the use of fluoroquinolones in treatment of community-acquired UTI. This has already been taken into account in the current National UTI guidelines lacking this antibiotic class [27]. According to the questionnaires Russia had the most patients hospitalized during the last 6 months (34.5%), which could also be a reason for the

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relatively high resistance rates of isolated *E. coli* since hospitalization during the last 6 months were identified as a risk factor in Russia in our analysis.

NoDARS results indicate that nitrofurantoin, fosfomycin and mecillinam were the most active oral antibiotics with susceptibility rates of 99%, 99% and 95.9%, respectively. Taking into consideration that mecillinam is not available in Russia (Table 6), our results strongly support currently available national recommendations to use nitrofurantoin and fosfomycin as the first line antibiotics for treatment of acute uncomplicated UTI [27].

In **Sweden** resistance rates were above 20% for trimethoprim, trimethoprim/sulfamethoxazole and ampicillin. The results for nitrofurantoin, trimethopirim and ciprofloxacin were similar to data for complicated UTI from national surveillance [28]. The number of suspected ESBL were similar between NoDARS (5.8%) and national data from complicated UTI (5.5%) and BSI (7.8%) [28].

The Swedish first line treatment recommendations for uncomplicated UTI were supported by the result of our study (Table 6). Sweden had one positive risk factor for high age (51-65) for patients that had a UTI caused by a ciprofloxacin resistant *E. coli*. Although the confidence interval was broad (1.3 to 193.1) this still indicates an increased risk for older patients.

4.3. Limitations

This study has limitations that are important to take into account. Since the number of collected *E. coli* isolates for some partners were low, there might be limitations in comparison of levels of resistance between certain countries. Also samplings were mainly done regionally which give possible limitations to extrapolate results nationwide. However, in Sweden and Finland that have countrywide data on complicated UTI, no major local differences in resistance patterns have been seen [20, 28]. Another possible limitation might be variations in collecting urine samples between countries with so dissimilar healthcare systems. However, the almost equal median and mean age of the patients confirm conformity of population and validity of the survey. Some patient had taken antibiotics and been hospitalised (Table 1) which might have increased the overall resistance rate. No multivariate analysis was performed it is hard to draw conclusions about risk factors since confounding could be an issue.

5. Conclusion

NoDARS resulted in a large and unique collection of *E. coli* isolates from outpatient women with UTI. Resistance patterns vary significantly among partner countries suggesting continuation of surveillance monitoring and further local epidemiological studies, which is mandatory for guideline updating and correct empirical therapy.

Although variations exist, we found antibiotics with good susceptibility (nitrofurantoin, mecillinam and fosfomycin) in all partner countries supporting the usefulness of international recommendations. Between- and within-country analysis demonstrated risk factors for prevalence of antibiotic resistant

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UTIs which provided more evidence to identify patient populations with potential treatment challenges.

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Competing Interests
None to declare

Ethical approval
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Table 1. Culture results and descriptive information for outpatients positive for *E. coli* UTI. Small variations from the total number were sometimes present due to that not all patients answered all questions. If the patient had travelled to more than one region during the past 6 months all the regions were noted. In total 14 UTI samples could not be analysed for unknown reasons.

Basic statistic	Finland	Germany	Latvia	Poland	Russia	Sweden	Total
Culture results							
Tot number of UTI samples	60	561	89	121	292	155	1278
Negative culture n (%)	26 (43.3)	173 (30.8)	18 (20.2)	16 (13.2)	8 (2.7)	34 (21.9)	275 (21.6)
Positive for bacteria other than *E. coli* n (%)	4 (6.7)	104 (18.5)	13 (14.6)	12 (9.9)	71 (24.3)	10 (6.5)	214 (16.8)
Positive for *E. coli* n (%)	30 (50)	284 (50.6)	58 (65.2)	95 (78.5)	197 (67.5)	89 (71.6)	775(58.9)
Descriptive information for patients positive for E. coli UTI							
Age mean (sd)	43 (13.7)	43 (14.5)	35 (12.2)	47(14.2)	42 (14.5)	40 (13.7)	42 (14.4)
Age median (q1;q3)	43 (31;54)	45 (30;56)	33 (28;39)	49 (34;61)	39 (29;57)	39 (27;51)	42 (29;55)
Antibiotic consumption during the last 12 months % (n)	50 (15)	NA	20.7 (12)	54.7 (52)	52.3 (103)	25.8 (23)	43.7 (205)
Hospitalization during the last 6 months % (n)	10 (3)	NA	6.9 (4)	10.6 (10)	34.5 (68)	2.2 (2)	18.6 (87)
Travel the last 6 months % (n)	56.7 (17)	NA	39.7 (23)	14.7 (14)	25.4 (50)	53.9 (48)	32.4 (152)
Eastern Europe % (n)	31.6 (6)	NA	25.5 (12)	5.8 (5)	12 (20)	10.9 (5)	13.2 (48)
Mediterranean Europe % (n)	35 (7)	NA	20.5 (9)	4.7 (4)	5.2 (8)	32.8 (20)	13.2 (48)
Nordic region % (n)	18.8 (3)	NA	5.4 (2)	1.2 (1)	0 (0)	12.8 (6)	3.6 (12)
Other Europe % (n)	13.3 (2)	NA	20.5 (9)	6.9 (6)	9.3 (15)	26.8 (15)	12.9 (47)
North Africa % (n)	0 (0)	NA	2.8 (1)	0 (0)	4.5 (7)	2.4 (1)	2.8 (9)
Sub-Saharan Africa % (n)	0 (0)	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Australia/New Zeeland % (n)	0 (0)	NA	0 (0)	0 (0)	0 (0)	4.7 (2)	0.6 (2)
Asia % (n)	13.3 (2)	NA	2.8 (1)	0 (0)	0 (0)	16.3 (8)	3.4 (11)
North America % (n)	7.1 (1)	NA	0 (0)	0 (0)	0 (0)	2.4 (1)	0.6 (2)
South America % (n)	0 (0)	NA	0 (0)	0 (0)	0 (0)	6.8 (3)	0.9 (3)

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Table 2. Resistance (resistant and intermediate R+I) in % with 95% confidence intervals for *E. coli* outpatient UTI-isolates. DM stands for data missing. MDR stands for Multi Drug Resistant

Substance	**Finland (n=30)**	**Germany (n=284)**	**Latvia (n=58)**	**Poland (n=95)**	**Russia (n=197)**	**Sweden (n=111)**	**Total (n=775)**
% (95% CI)							
Single resistance							
Amoxicillin/ clavulanic acid	0 (0-11.6)	32.9 (25.2-41.3)	1.7 (0-9.2)	11.6 (5.9-19.8)	18.8 (13.3-24.9)	8.9 (4.2-16.2)	16.7 (13.9-19.9)
Ampicillin	20 (7.7-38.6)	35.0 (27.1-43.5)	36.2 (24-49.9)	45.3 (35.0-55.8)	44.2 (37.1-51.34)	39.3 (30-49.2)	39.6 (35.7-43.5)
Cefotaxime	0 (0-11.6)	4.3 (2.0-8.1)	0 (0-6.2)	7.4 (3.0-14.6)	15.7 (10.9-21.6)	5.8 (2.1-12.1)	7.7 (5.8-9.9)
Ceftazidime	0 (0-11.6)	6.1 (3.6-9.6)	0 (0-6.2)	6.3 (2.4-13.2)	13.7 (9.2-19.3)	5.6 (2.1-11.8)	7.3 (5.6-9.4)
Cefoxitin	0 (0-11.6)	DM	0 (0-6.2)	3.2 (0.7-9.0)	4.6 (2.1-8.5)	2.9 (0.6-8.2)	3.1 (1.7-5.1)
Cefuroxime	0 (0-11.6)	7.2 (4.4-10.9)	1.7 (0-9.2)	8.4 (3.7-15.9)	17.8 (12.7-23.8)	9.0 (4.2-16.4)	9.6 (7.6-11.9)
Ciprofloxacin	13.3 (3.8-30.7)	6.1 (3.6-9.6)	5.2 (1.1-14.4)	25.3 (16.9-35.2)	28.4 (22.2-35.3)	11.1 (5.9-18.6)	15.1 (12.7-17.9)
Fosfomycin	3.3 (0.1-17.2)	1.1 (0.2-3.1)	3.4 (0.4-11.9)	0 (0-3.8)	1.0 (0.1-3.6)	2 (0.2-7.1)	1.3 (0.6-2.4)
Gentamicin	3.3 (0.1-17.2)	3.9 (2.0-6.9)	1.7 (0-9.2)	5.3 (1.7-11.9)	12.7 (8.4-18.2)	7.7 (3.4-14.6)	6.7 (5.0-8.7)
Mecillinam	3.3 (0.1-17.2)	DM	1.7 (0-9.2)	10.5 (5.2-18.5)	4.1 (1.8-7.8)	0 (0-3.4)	4.1 (2.5-6.3)
Meropenem	0 (0-11.6)	0 (0-1.3)	0 (0-6.2)	0 (0-3.8)	0 (0-1.9)	0 (0-4.1)	0 (0-0.5)
Nitrofurantoin	0 (0-11.6)	0.4 (0-2.0)	0 (0-6.2)	6.3 (2.4-13.2)	1.0 (0.1-3.6)	0 (0-3.4)	1.2 (0.5-2.2)
Trimethoprim	20 (7.7-38.6)	18.4 (13.9-23.6)	25.9 (15.3-39.0)	32.6 (23.4-43.0)	27.4 (21.3-34.2)	22.4 (14.9-31.5)	23.8 (20.8-27.0)
Trimethoprim/ sulfamethoxazole	20 (7.7-38.6)	16.1 (12.0-21.0)	24.1 (13.9-37.2)	31.6 (22.4-41.9)	26.4 (20.4-33.1)	22.9 (15.2-32.1)	22.4 (19.5-25.5)
Combination resistance							

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MDR	10.0 (2.1-26.5)	7.0 (4.4-10.7)	1.7 (0-9.2)	18.9 (11.6-28.3)	26.9 (20.8-33.7)	11.7 (6.4-19.2)	13.9 (11.6-16.6)
ESBL	0 (0-11.6)	7.9 (4.7-12.4)	0 (0-6.2)	7.4 (3-14.6)	15.7 (10.9-21.9)	5.8 (2.1-12.1)	8.7 (6.7-11.1)
Cipro+gentamicin	3.3 (0.1-17.2)	2.2 (0.8-4.6)	1.7 (0-9.2)	5.3 (1.7-11.9)	11.2 (7.1-16.4)	2.9 (0.6-8.2)	5.0 (3.5-6.8)
ESBL+ciprofolxacin	0 (0-11.6)	3.7 (1.6-7.2)	0 (0-6.2)	4.2 (1.2-10.4)	12.2 (8.0-17.6)	2.9 (0.6-8.2)	5.6 (4.0-7.5)
ESBL+gentamicin	0 (0-11.6)	3.3 (1.3-6.6)	0 (0-6.2)	2.1 (0.3-7.4)	7.1 (3.9-11.6)	0 (0-3.5)	3.3 (2.1-4.9)
ESBL+ciprofloxacin+gentamicin	0 (0-11.6)	1.9 (0.5-4.7)	0 (0-6.2)	2.1 (0.3-7.4)	6.6 (3.6-11.0)	0 (0-3.5)	2.7 (1.6-4.2)

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Table 3. Univariate logistic regression analysis of risk factors within and between partner countries for ciprofloxacin resistant and intermediate (R+I) *E. coli* in outpatient UTI. NA was written when the analysis was not relevant or we could not perform the analysis due zero cases in the comparison, DM was written when data was missing, Ref is the reference value used for calculation in a given category. Statistically significant results are in bold text. In the within-country analysis each risk factor is investigated per country. In the between-countries analysis each country is investigated as risk factor for each patient population/sub-population.

Risk factors/Sub populations	**Country**	**Total number of isolates**	**Ciprofloxacin resistance (R+I) % (n)**	**Within-country OR (95% CI)**	**Between-countries OR (95% CI)[a]**
Total resistance					
Ciprofloxacin	Finland	30	13.3 (4)	NA	1.4 (0.4 to 3.5)
	Germany	262	3.4 (9)	NA	**0.2 (0.1 to 0.4)**
	Latvia	58	5.2 (3)	NA	0.5 (0.1 to 1.3)
	Poland	88	22.7 (20)	NA	**2.9 (1.6 to 5.0)**
	Russia	166	19.3 (32)	NA	**2.6 (1.6 to 4.2)**
	Sweden	81	9.9 (8)	NA	0.9 (0.4 to 1.8)
Age					
18-30	Finland	8	0	NA	NA
	Germany	72	0	NA	NA
	Latvia	24	0	NA	NA
	Poland	15	13.3 (2)	Ref	3.1 (0.4 to 11.9)
	Russia	55	16.4 (9)	Ref	**7.1 (2.3 to 29.2)**
	Sweden	27	3.7 (1)	Ref	0.8 (<0.1 to 3.5)
	All countries	201	6.0 (12)	Ref	NA
31-50	Finland	13	23.1 (3)	NA	NA
	Germany	95	3.2 (3)	NA	NA
	Latvia	24	0	NA	NA
	Poland	33	21.2 (7)	1.5 (0.3 to 12.9)	**4.2 (1.5 to 10.7)**
	Russia	63	12.7 (8)	0.7 (0.3 to 2.1)	2.1 (0.8 to 5.1)
	Sweden	32	3.1 (1)	0.8 (<0.1 to 21.9)	0.5 (<0.1 to 2.0)
	All countries	260	8.5 (22)	1.4 (0.7 to 3.1)	NA
51-65	Finland	9	11.1 (1)	NA	NA

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	Germany	95	6.3 (6)	NA	NA
	Latvia	9	33.3 (3)	NA	NA
	Poland	40	27.5 (11)	2.1 (0.5 to 17.4)	2 (0.9 to 4.3)
	Russia	48	31.2 (15)	2.3 (0.9 to 6.1)	**2.6 (1.2 to 5.5)**
	Sweden	22	27.3 (6)	**7.0 (1.3 to 193.1)**	1.9 (0.6 to 4.8)
	All countries	223	18.8 (42)	**3.5 (1.9 to 7.5)**	NA
Antibiotic treatment during last 12 months					
No	Finland	15	6.7 (1)	Ref	Ref
	Germany[b]	DM	DM	DM	DM
	Latvia	45	6.7 (3)	NA	NA
	Poland	37	10.8 (4)	Ref	Ref
	Russia	82	13.4 (11)	Ref	Ref
	Sweden	52	11.5 (6)	Ref	Ref
	All countries	231	10.8 (25)	Ref	NA
Yes	Finland	15	20 (3)	2.7 (0.4 to 76.1)	0.9 (0.2 to 2.9)
	Germany[b]	DM	DM	DM	DM
	Latvia	12	0 (0)	NA	NA
	Poland	46	34.8 (16)	**4.0 (1.4 to 16.7)**	**2.3 (1.1 to 4.9)**
	Russia	80	23.8 (19)	2.0 (0.9 to 4.7)	1.1 (0.5 to 2.2)
	Sweden	21	9.5 (2)	0.9 (0.1 to 4.0)	0.4 (<0.1 to 1.3)
	All countries	174	23.0 (40)	**2.4 (1.4 to 4.3)**	NA
Hospitalization during last 6 months					
No	Finland	27	14.8 (4)	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	54	3.7 (2)	Ref	Ref
	Poland	78	21.8 (17)	Ref	Ref
	Russia	122	13.9 (17)	Ref	Ref
	Sweden	78	10.3 (8)	NA	NA
	All countries	359	13.4 (48)	Ref	NA
Yes	Finland	3	0	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	4	25 (1)	9.0 (0.3 to 122.8)	1 (<0.1 to 6.8)

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	Poland	9	22.2 (2)	1.2 (0.1 to 4.9)	0.8 (0.1 to 3.2)
	Russia	44	34.1 (15)	**3.2 (1.4 to 7.2)**	2.3 (0.7 to 12.4)
	Sweden	2	0	NA	NA
	All countries	62	29.0 (18)	**2.4 (1.4 to 4.9)**	NA

[a] Comparison of resistance numbers from each individual country compared with the other countries. The comparison group used as reference was the total number for all countries minus the country investigated.
[b] Germany missing results for antibiotic treatment and hospitalization

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Table 4. Univariate logistic regression analysis of risk factors within and between partner countries for ESBL-producing *E. coli* in outpatient UTI. NA was written when the analysis was not relevant or we could not perform the analysis due zero cases in the comparison, DM was written when data was missing, Ref is the reference value used for calculation in a given category. Statistically significant results are in bold text. In the within-country analysis each risk factor is investigated per country. In the between-countries analysis each country is investigated as risk factor for each patient population/sub-population.

Risk factors/ Sub-populations	**Country**	**Total number of isolates**	**ESBL-producing *E. coli* % (n)**	**Within-country OR (95% CI)**	**Between-countries OR (95% CI)[a]**
Total resistance					
ESBL	Finland	30	0	NA	NA
	Germany	215	7.9 (17)	NA	0.8 (0.4 to 1.5)
	Latvia	58	0	NA	NA
	Poland	95	7.4 (7)	NA	0.8 (0.3 to 1.7)
	Russia	197	15.7 (31)	NA	**2.8 (1.6 to 4.8)**
	Sweden	83	7.2 (6)	NA	0.8 (0.3 to 1.8)
Age					
18-30	Finland	8	0	NA	NA
	Germany	61	4.9 (3)	Ref	1.4 (0.3 to 5.5)
	Latvia	24	0	NA	NA
	Poland	16	6.2 (1)	Ref	2.8 (0.1 to 12)
	Russia	58	5.2 (3)	Ref	1.7 (0.3 to 6.6)
	Sweden	26	3.8 (1)	Ref	1.4 (0.1 to 6.6)
	All countries	193	4.1 (8)	Ref	NA
31-50	Finland	13	0	NA	NA
	Germany	73	9.6 (7)	1.9 (0.5 to 9.8)	1.2 (0.4 to 2.9)
	Latvia	24	0	NA	NA
	Poland	35	5.7 (2)	0.8 (0.1 to 20.4)	0.8 (0.1 to 2.5)
	Russia	73	13.7 (10)	2.6 (0.8 to 13.5)	**2.4 (1.0 to 5.8)**
	Sweden	33	9.1 (3)	2.0 (0.3 to 52.3)	1.3 (0.3 to 3.8)
	All countries	251	8.8 (22)	**2.1 (1.0 to 5.4)**	NA
51-65	Finland	9	0	NA	NA
	Germany	81	8.6 (7)	1.7 (0.5 to 8.8)	0.5 (0.2 to 1.2)
	Latvia	24	0	NA	NA
	Poland	44	9.1 (4)	1.1 (0.2 to 30.6)	0.7 (0.2 to 1.8)
	Russia	66	27.3 (18)	**6.0 (2.0 to 30.6)**	**4.8 (2.2 to 11.2)**
	Sweden	24	8.3 (2)	1.9 (0.2 to 50.9)	0.7 (0.1 to 2.4)
	All countries	233	13.3 (3)	**3.4 (1.6 to 8.5)**	NA
Antibiotic treatment during last 12 months					
No	Finland	15	0	NA	NA

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	Germany[b]	DM	DM	DM	DM
	Latvia	45	0	NA	NA
	Poland	38	2.6 (1)	Ref	Ref
	Russia	90	8.9 (8)	Ref	Ref
	Sweden	52	7.7 (4)	Ref	Ref
	All countries	240	5.4 (13)	Ref	NA
Yes	Finland	15	0	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	12	0	NA	NA
	Poland	52	11.5 (6)	3.5 (0.7 to 93.2)	0.7 (0.2 to 1.7)
	Russia	103	22.3 (23)	**2.8 (1.3 to 7.4)**	**3.2 (1.5 to 8.4)**
	Sweden	23	8.7 (2)	1.3 (0.2 to 6.3)	0.6 (0.1 to 2.0)
	All countries	205	15.1 (31)	**3.0 (1.6 to 6.3)**	NA
Hospitalization during last 6 months					
No	Finland	27	0	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	54	0	NA	NA
	Poland	84	7.1 (6)	Ref	Ref
	Russia	129	5.4 (7)	Ref	Ref
	Sweden	80	7.5 (6)	NA	NA
	All countries	374	5.1 (19)	Ref	NA
Yes	Finland	3	0	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	4	0	NA	NA
	Poland	10	10 (1)	1.9 (0.1 to 10.6)	0.3 (<0.1 to 1.6)
	Russia	68	35.3 (24)	**9.0 (3.9 to 25.3)**	**6.8 (1.6 to 182.0)**
	Sweden	2	0	NA	NA
	All countries	87	28.7 (25)	**7.4 (3.9 to 14.7)**	NA

[a] Comparison of resistance numbers from each individual country compared with the other countries. The comparison group used as reference was the total number for all countries minus the country investigated.

[b] Germany missing results for antibiotic treatment and hospitalization

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Table 5. Univariate logistic regression analysis of risk factors within and between partner countries for MDR (Multi Drug Resistant) *E. coli* in outpatient UTI. NA was written when the analysis was not relevant or we could not perform the analysis due zero cases in the comparison, DM was written when data was missing, Ref is the reference value used for calculation in a given category. Statistically significant results are in bold text. In the within-country analysis each risk factor is investigated per country. In the between-countries analysis each country is investigated as risk factor for each patient population/sub-population.

Risk factors/sub-populations	**Country**	**Total number of isolates**	**MDR *E. coli* % (n)**	**Within-country OR (95% CI)**	**Between-countries OR (95% CI)[a]**
Total resistance					
MDR	Finland	30	10 (3)	NA	0.8 (0.2 to 2.1)
	Germany	248	7 (20)	NA	**0.3 (0.2 to 0.6)**
	Latvia	68	1.7 (1)	NA	**0.1 (<0.1 to 0.5)**
	Poland	95	18.9 (18)	NA	1.5 (0.8 to 2.6)
	Russia	197	26.9 (53)	NA	**3.4 (2.2 to 5.2)**
	Sweden	89	13.5 (12)	NA	1.0 (0.5 to 1.8)
Age					
18-30	Finland	8	0	NA	NA
	Germany	75	2.7 (2)	Ref	0.3 (<0.1 to 1.1)
	Latvia	24	0	NA	NA
	Poland	16	12.5 (2)	Ref	2.5 (0.3 to 9.4)
	Russia	58	13.8 (8)	Ref	**3.6 (1.2 to 10.8)**
	Sweden	29	10.3 (3)	Ref	1.9 (0.4 to 6.2)
	All countries	210	7.1 (15)	Ref	NA
31-50	Finland	13	15.4 (2)	NA	NA
	Germany	105	5.7 (6)	1.9 (0.5 to 15.4)	**0.4 (0.1 to 0.9)**
	Latvia	24	0	NA	NA
	Poland	35	11.4 (4)	0.8 (0.2 to 7.1)	1.4 (0.4 to 3.8)
	Russia	73	23.3 (17)	1.8 (0.5 to 5.0)	**5.8 (2.6 to 13.7)**
	Sweden	35	5.7 (2)	0.6 (0.1 to 3.4)	0.7 (0.1 to 2.2)
	All countries	285	10.9 (31)	1.6 (0.8 to 3.1)	NA
51-65	Finland	9	11.1 (1)	NA	NA
	Germany	104	11.5 (12)	4.0 (1.1 to 31.2)	**0.3 (0.1 to 0.5)**
	Latvia	9	11.1 (1)	NA	NA
	Poland	44	27.3 (12)	2.2 (0.6 to 18.3)	1.4 (0.6 to 2.8)
	Russia	35	42.4 (28)	**4.4 (1.9 to 11.9)**	**3.9 (2.1 to 7.4)**
	Sweden	25	28 (7)	3.1 (0.8 to 17.3)	1.4 (0.5 to 3.4)
	All countries	257	23.7 (61)	**3.9 (2.2 to7.6)**	NA
Antibiotic treatment during last 12 months					
No	Finland	15	0	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	45	2.2 (1)	NA	NA
	Poland	38	7.9 (3)	Ref	Ref
	Russia	90	13.3 (12)	Ref	Ref
	Sweden	57	14 (8)	Ref	Ref
	All countries	245	9.8 (24)	Ref	NA
Yes	Finland	15	20 (3)	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	12	0	NA	NA
	Poland	52	28.8 (15)	**4.2 (1.3 to 21.7)**	1 (0.5 to 1.9)
	Russia	103	37.9 (39)	**3.8 (1.9 to 8.5)**	**2.3 (1.3 to 4.4)**
	Sweden	23	13 (3)	1 (0.2 to 3.6)	0.4 (0.1 to 1.1)
	All countries	205	29.3 (60)	**3.8 (2.3 to 6.5)**	NA

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Hospitalization during last 6 months					
No	Finland	27	11.1 (3)	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	54	1.9 (1)	NA	NA
	Poland	84	16.7 (14)	Ref	Ref
	Russia	129	14.7 (19)	Ref	Ref
	Sweden	86	14 (12)	NA	NA
	All countries	380	12.9 (49)	Ref	NA
Yes	Finland	3	0	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	4	0	NA	NA
	Poland	10	30 (3)	2.3 (0.4 to 8.8)	0.6 (0.1 to 2.1)
	Russia	68	50 (34)	**5.7 (2.9 to 11.6)**	**4.7 (1.5 to 24.4)**
	Sweden	2	0	NA	NA
	All countries	87	42.5 (37)	5.0 (3.0 to 8.4)	NA

[a] Comparison of resistance numbers from each individual country compared with the other countries. The comparison group used as reference was the total number for all countries minus the country investigated.
[b] Germany missing results for antibiotic treatment and hospitalization

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Table 6. Summary of national treatment guidelines for uncomplicated UTI and availability of antibiotics tested in partner countries.

Questions	Finland	Latvia	Germany	Poland	Russia	Sweden
National treatment guidelines						
National guideline present	Yes	No	Yes	Yes	Yes	Yes
Year first implemented	2000	-	2010	2015	2017	2007
Year of latest revision	2015	-	2017	-	-	2017
Type of surveillance data as basis	Continuous national collections	-	Observational studies, continuous national collections	Several point-prevalence studies	Point-prevalence study 2011	Continuous national collections
Recommended first line						
Fosfomycin		-	Yes	Yes	Yes	
Furazidin		-		Yes	Yes	
Mecillinam	Yes	-	Yes			Yes
Nitrofurantoin	Yes	-	Yes	Yes	Yes	Yes
Nitroxolin		-	Yes			
Trimethoprim	Yes	-	Yes[a]	Yes		
Trimethoprim-sulfamethoxazole		-		Yes		
Recommended second line						
Amoxicillin	Yes	-				
Amoxicillin-clavulanic acid	Yes	-		Yes		
Cefadroxil	Yes	-				Yes
Cefalexin	Yes	-				
Cefixime		-			Yes	
Cefpodoxim-Proxetil		-	Yes			
Ceftibuten		-			Yes	
Ciprofloxacin	Yes	-	Yes	Yes	Yes	
Levofloxacin	Yes	-	Yes	Yes	Yes	
Norfloxaxin		-	Yes			
Ofloxacin	Yes	-	Yes	Yes	Yes	
Trimethoprim		-				Yes[a]
Trimethoprim/sulfamethoxazole		-	Yes			
Availability of NoDARS antibiotics						
Ampicillin	Yes	Yes	Yes	Yes[c]	Yes	Yes
Amoxicillin clavulanic acid	Yes	Yes	Yes	Yes	Yes	Yes
Cefuroxime	Yes	Yes	Yes	Yes	Yes	Yes
Ciprofloxacin	Yes	Yes	Yes	Yes	Yes	Yes
Fosfomycin	No[b]	No[b]	Yes	Yes[c]	Yes	No[e]
Nitrofurantoin	Yes	Yes	Yes	No[d]	Yes	Yes
Mecillinam	Yes	No[b]	Yes	No[b]	No[b]	Yes
Trimethoprim	Yes	Yes	Yes	Yes[c]	No[b]	Yes
Trimethoprim-sulfamethoxazole	Yes	Yes	Yes	Yes	Yes	Yes

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[a] Only use if resistance of isolate is known
[b] Not licensed
[c] Not reimbursed
[d] Furazidin a nitrofurantoin like substance is available without prescription
[e] Fosfomycin licenced but only for specific indications

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