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Antimicrobial resistance of *Escherichia coli* isolates from outpatient urinary tract infections in women in six European countries including Russia

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ABSTRACT

Objectives: In the Northern Dimension Antibiotic Resistance Study (NoDARS), Finland, Germany, Latvia, Poland, Russia and Sweden collected urine samples from outpatient women (aged 18–65 years) with symptoms of uncomplicated urinary tract infection (UTI) to investigate the levels of antimicrobial resistance (AMR) among *Escherichia coli* isolates.
Methods: A total of 775 *E. coli* isolates from 1280 clinical urine samples were collected from October 2015 to January 2017. Antimicrobial susceptibility testing was performed and the results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.
Results: Overall AMR rates to the commonly used antibiotics nitrofurantoin, fosfomycin and mecillinam (except for Germany that was missing a result for mecillinam) were 1.2%, 1.3% and 4.1%, respectively. The highest overall resistance rates were determined for ampicillin (39.6%), trimethoprim (23.8%), trimethoprim/sulfamethoxazole (22.4%), amoxicillin/clavulanic acid (16.7%) and ciprofloxacin (15.1%), varying significantly between countries. The rate of extended-spectrum β-lactamase (ESBL) production was 8.7%. None of the isolates showed resistance to meropenem.
Conclusions: In most cases, low AMR rates were detected against the first-line antibiotics recommended in national UTI treatment guidelines, giving support to their future use. These results also support the European Association of Urology guidelines stating that nitrofurantoin, fosfomycin and mecillinam are viable treatment options for uncomplicated UTI.

1. Introduction

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

In many countries, the practice is to start empirical antibiotic treatment without urine culture and antimicrobial susceptibility testing (AST). Recommendations for empirical treatment are often based on AST results of samples taken from complicated UTIs caused by *E. coli*. However, patients with complicated UTI often possess risk factors such as older age, prior antibiotic treatment and previous hospitalisation. Thus, the pathogens isolated may show much higher levels of antimicrobial resistance (AMR) [3–5].

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On the other hand, there are also studies showing that the levels of colonisation with extended-spectrum β-lactamase (ESBL)-producing isolates in healthy carriers are increasing in the community [6,7]. This trend is also seen in bloodstream infections in many European countries [8]. To avoid driving the development and spread of AMR, it is important to treat patients with narrow-spectrum antibiotics that show good susceptibility in the local *E. coli* population. Some antibiotics such as 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 data on the resistance levels of *E. coli* isolates causing uncomplicated UTIs are therefore critically needed.

Thus, we aimed to investigate the levels of AMR 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-resistant and/or multidrug-resistant (MDR) isolates, data on age, antibiotic consumption during the last 12 months, hospitalisation during the last 6 months and travel history were also collected. Data on current national/international treatment recommendations in each partner country were also reviewed in comparison with the AMR levels detected.

2. Materials and methods

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 obtained from each patient.

Women aged 18–65 years (including pregnant women) with at least two of the following specified symptoms were included in the study: dysuria; frequent urgency and/or increased urinary frequency in the absence of vaginal symptoms (such as abnormal discharge, itching and/or inflammation of the vulva); fever; and flank pain. Exclusion criteria were consumption of any kind of antibiotic for any indication during the last 3 months before the date of enrolment in the study. An exception from this was Germany, which excluded only patients who had received antibiotics in the last 2 weeks, and Poland and Finland, which included some patients who had received antibiotics the last 2 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, Turku region (2 sites); Latvia, Riga region (15 sites); Germany, regions of Berlin, Schleswig-Holstein, North Rhine-Westphalia and Baden-Württemberg (58 sites); Poland, Silesian Voivodeship (1 site); Russia, six geographically distant cities representing European and Asian parts of Russia (12 sites); and Sweden, Stockholm region (7 sites). German data were 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, hospitalisation during the last 6 months, and travel abroad along with travel destination (Supplementary file S1).

Data on the presence of national guidelines for the treatment of uncomplicated UTIs 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

Urine samples were cultured based on internationally accepted standards [13]. 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 European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology and breakpoints (http://www.eucast.org/; accessed 15 February 2018). The resistance rate was defined as the percentage of non-susceptible (resistant + intermediate) isolates to the antibiotic in question. An ESBL phenotype was defined as resistant and/or intermediate to cefotaxime and/or ceftazidime. MDR was defined as resistance to three or more classes of antibiotics defined as follows: (i) nitrofurantoin; (ii) ampicillin, mecillinam; (iii) amoxicillin/clavulanic acid (AMC); (iv) cefotaxime, ceftazidime, cefuroxime; (v) meropenem; (vi) trimethoprim, trimethoprim/sulfamethoxazole (SXT); (vii) fosfomycin; (viii) ciprofloxacin; and (ix) gentamicin [14].

2.3. Statistical analyses

Univariate risk analyses were performed only for patients who both contributed a sample and a questionnaire and who were positive for *E. coli* UTI. Firth's logistic regression model was used to calculate odd ratios (ORs) and 95% confidence intervals (CIs) for the risk analyses. No multivariate analysis was performed. Risk analyses for having a UTI with specific resistance determinants were performed both from within-country and between-countries perspectives. In the within-country analysis, risk factors (e.g. hospitalisation versus non-hospitalisation) in each partner country were investigated. In the between-countries analysis, the patient population from each country as well as subpopulations (divided based on age, antibiotic treatment and hospitalisation) were compared with the same population/subpopulation in all other partner countries combined. The between-countries analysis was performed to investigate whether some patient populations had a higher risk of having resistant isolates compared with other partner countries combined. All statistical analyses were performed in R statistical software v.3.2.5.

3. Results

3.1. Sample collection

A total of 1280 urine samples from patients with symptoms of lower UTI were collected, resulting in 21.6% (276/1280) negative cultures, 17.9% (229/1280) cultures that were positive for other bacterial species, and 60.5% ($n = 775$ *E. coli* isolates) that underwent AST (Table 1; Supplementary Fig. S1). In total, *E. coli* caused 77.2% of culture-positive infections. A total of 725 questionnaires were available for analysis, of which 469 were from patients with *E. coli* isolated and were therefore used in the risk analyses. 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 who had received 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 received antibiotics during the last 3 months. Also for the Polish patients, 12% ($n = 11$) were receiving antibiotics at the time of enrolment in the study. Hospitalisation during the last 6 months varied between partner countries, ranging from 2% (Sweden) to 35% (Russia). Data on travel during the last 6 months are presented descriptively

Table 1
Culture results and descriptive information for outpatients positive for *Escherichia coli* urinary tract infection (UTI). Small variations from the total number were sometimes present due to the fact that not all patients answered all questions. If the patient had travelled to more than one region during the past 6 months, all of the regions were noted.

Basic statistic	Finland	Germany	Latvia	Poland	Russia	Sweden	Total
Culture results							
Total no. of UTI samples	60	561	89	123	292	155	1280
Negative culture [*n* (%)]	26 (43.3)	173 (30.8)	18 (20.2)	16 (13.0)	9 (3.1)	34 (21.9)	276 (21.6)
Positive for bacteria other than *E. coli* [*n* (%)]	4 (6.7)	104 (18.5)	13 (14.6)	12 (9.8)	86 (29.5)	10 (6.5)	229 (17.9)
Positive for *E. coli* [*n* (%)]	30 (50.0)	284 (50.6)	58 (65.2)	95 (77.2)	197 (67.5)	111 (71.6)	775 (60.5)
Descriptive information for patients positive for *E. coli* UTI							
No. of subjects positive for *E. coli* who answered questionnaire	30	NA	58	95	197	89	469
Age (mean ± S.D.)	43 ± 13.7	43 ± 14.5	35 ± 12.2	47± 14.2	42 ± 14.5	40 ± 13.7	42 ± 14.4
Age [median (IQR)]	43 (31–54)	45 (30–56)	33 (28–39)	49 (34–61)	39 (29–57)	39 (27–51)	42 (29–55)
Antibiotic consumption during last 12 months [% (*n*)]	50.0 (15)	NA	20.7 (12)	54.7 (52)	52.3 (103)	25.8 (23)	43.7 (205)
Hospitalisation during last 6 months [% (*n*)]	10.0 (3)	NA	6.9 (4)	10.5 (10)	34.5 (68)	2.2 (2)	18.6 (87)
Travel during 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	20.0 (6)	NA	20.7 (12)	5.3 (5)	10.2 (20)	5.6 (5)	10.2 (48)
Mediterranean Europe	23.3 (7)	NA	15.5 (9)	4.2 (4)	4.1 (8)	22.5 (20)	10.2 (48)
Nordic region	10.0 (3)	NA	3.4 (2)	1.1 (1)	0 (0)	6.7 (6)	2.6 (12)
Other Europe	6.7 (2)	NA	15.5 (9)	6.3 (6)	7.6 (15)	16.9 (15)	10.0(47)
North Africa	0 (0)	NA	1.7 (1)	0 (0)	3.6 (7)	1.1 (1)	1.9 (9)
Sub-Saharan Africa	0 (0)	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Australia/New Zealand	0 (0)	NA	0 (0)	0 (0)	0 (0)	2.2 (2)	0.4 (2)
Asia	6.7 (2)	NA	1.7 (1)	0 (0)	0 (0)	9.0 (8)	2.3 (11)
North America	3.3 (1)	NA	0 (0)	0 (0)	0 (0)	1.1 (1)	0.4 (2)
South America	0 (0)	NA	0 (0)	0 (0)	0 (0)	3.4 (3)	0.6 (3)

S.D. standard deviation; IQR, interquartile range; NA, not available.

owing to the low numbers of travellers. Travel abroad varied between partner countries from 15% (Poland) to 57% (Finland), with the most common destination being Eastern and Mediterranean Europe (Table 1).

3.3. *Antimicrobial resistance of* Escherichia coli *isolates*

Table 2 shows the non-susceptibility rates 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 the collected *E. coli* isolates was detected. The highest rates of resistance were found for ampicillin (39.6%), trimethoprim (23.8%), SXT (22.4%) and AMC (16.7%). More than 15% of all *E. coli* showed resistance to ciprofloxacin. In total, 13.9% and 8.7% of isolates had a MDR and/or ESBL phenotype, respectively (Table 2).

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 SXT (31.6%) among the partner countries were observed in Poland. An 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. 8.7% for all countries). The MDR rate ranged from 1.7% (Latvia) to 26.9% (Russia).

Table 2
Rate of non-susceptibility (resistant + intermediate) for *Escherichia coli* outpatient urinary tract infection isolates.

Antimicrobial agent	Percentage resistance (95% CI)						
	Finland (*n* = 30)	Germany (*n* = 284)	Latvia (*n* = 58)	Poland (*n* = 95)	Russia (*n* = 197)	Sweden (*n* = 111)	Total (*n* = 775)
Single resistance							
AMC	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)
SXT	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)
Combined resistance							
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)
Ciprofloxacin + 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 + ciprofloxacin	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)

CI, confidence interval; AMC, amoxicillin/clavulanic acid; DM, data missing; SXT, trimethoprim/sulfamethoxazole; MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase.

3.4. Risk analyses

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

For all partner countries combined, significant risk factors of acquiring a ciprofloxacin-resistant *E. coli* isolate were: age 51–65 years versus 18–30 years; previous antibiotic treatment during last 12 months; and previous hospitalisation during last 6 months (Table 3).

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

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

Between-countries analysis of subpopulations showed a higher risk of ciprofloxacin resistance for Polish patients who had previously received antibiotics during the last 12 months and patients in the age group 31–50 years. Russian patients in the age groups 18–30 years and 51–65 years also had a higher risk of ciprofloxacin resistance compared with patients in the same age groups from other partner countries (Table 3).

For all partner countries combined, significant risk factors for having an ESBL-producing *E. coli* as a cause of UTI were: age 31–65 years versus 18–30 years; previous antibiotic treatment during last 12 months; and previous hospitalisation during last 6 months. Within-country analysis showed significance for ESBL production for age 51–65 years, previous antibiotic treatment during last 12 months and previous hospitalisation during last 6 months only in Russia. Between-countries analysis showed that Russian patients had an increased risk of having an ESBL-producing *E. coli* in outpatient UTI compared with patients in other partner countries, which was also confirmed by a significantly higher risk in all subpopulations of Russian patients except for the age group 18–30 years (Table 4).

For all partner countries combined, significant risk factors for having a MDR *E. coli* UTI were age 51–65 years and previous antibiotic treatment during last 12 months. Further within-country analysis showed significance for age 51–65 years and previous hospitalisation during last 6 months for Russia only, and for previous antibiotic treatment during last 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 patients but was significantly lower in German and Latvian patients compared with patients in other partner countries. Moreover, between-countries analysis of subpopulations and factors showed significantly lower risks of MDR *E. coli* for German patients in the age groups 31–50 years and 51–65 years (Table 5).

3.5. Treatment recommendations

The structured survey of national treatment guidelines and availability of antibiotics showed that all partner countries 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 (SXT and trimethoprim) of five antibiotics recommended as first-line that had a resistance level reaching 30% in the current study. Otherwise, the AMR rates detected and compared with 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 its analogue furazidin was available over-the-counter instead (Table 6).

4. Discussion

NoDARS provides data on the current susceptibility of the uropathogen *E. coli* causing outpatient UTIs from six countries, namely Finland, Latvia, Germany, Poland, Russia and Sweden. The major strength of the NoDARS was the joint involvement of countries both from northern and eastern Europe with different AMR situations, healthcare system organisations 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 (<10% for partner countries in total), supporting the guidelines from the European Association of Urology recommending fosfomycin, nitrofurantoin and mecillinam as first-line treatments for uncomplicated UTIs [4]. Studies of AMR rates form the basis for decisions on empirical therapy options and also provide input for formulating and updating local and national treatment or 'best practice guidelines'.

However, there are no universal upper threshold values for when a certain antibiotic 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 SXT) or 10% (for fluoroquinolones) [15,16]. Fluoroquinolone resistance rates >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 infections (Table 2), especially since it also a known driver of multidrug resistance [9–11]. Resistance to SXT was around or above 20% in all partner countries (Table 2). Although there are studies supporting the use of SXT as 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 UTIs that allows between-countries comparison of the antimicrobial susceptibility of the causative microbe has previously been performed in other settings [18,19]. However, in NoDARS risk factors and risk populations were further investigated, 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 with patients from other partner countries (Tables 3–5).

Furthermore, risk factors for acquiring a resistant pathogen within each country were investigated. Older 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 for having a UTI with ESBL-producing and/or MDR *E. coli*. Poland also had a higher risk of ciprofloxacin-resistant and MDR *E. coli* in patients who had received antibiotics (Tables 3–5).

4.2. Country-by-country resistance rates

To analyse the findings and how they correlate with/support currently available national guidelines, we discuss the results country by country below.

Table 3
Univariate logistic regression analysis of risk factors within and between partner countries for ciprofloxacin-non-susceptible (CIP^{NS}) (resistant + intermediate) *Escherichia coli* outpatient urinary tract infection isolates.

Risk factor/subpopulation	Country	Total no. of isolates	CIP^{NS} [% (*n*)]	Within-country OR (95% CI)	Between-countries OR (95% CI)[a]
Total resistance					
Ciprofloxacin	Finland	30	13.3 (4)	NA	1.4 (0.4–3.5)
	Germany	262	3.4 (9)	NA	0.2 (0.1–0.4)
	Latvia	58	5.2 (3)	NA	0.5 (0.1–1.3)
	Poland	88	22.7 (20)	NA	2.9 (1.6–5.0)
	Russia	166	19.3 (32)	NA	2.6 (1.6–4.2)
	Sweden	81	9.9 (8)	NA	0.9 (0.4–1.8)
Age					
18–30 years	Finland	8	0	NA	NA
	Germany	72	0	NA	NA
	Latvia	24	0	NA	NA
	Poland	15	13.3 (2)	Ref.	3.1 (0.4–11.9)
	Russia	55	16.4 (9)	Ref.	**7.1 (2.3–29.2)**
	Sweden	27	3.7 (1)	Ref.	0.8 (<0.1–3.5)
	All countries	201	6.0 (12)	Ref.	NA
31–50 years	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 (0.3–12.9)	**4.2 (1.5–10.7)**
	Russia	63	12.7 (8)	0.7 (0.3–2.1)	2.1 (0.8–5.1)
	Sweden	32	3.1 (1)	0.8 (< 0.1–21.9)	0.5 (< 0.1–2.0)
	All countries	260	8.5 (22)	1.4 (0.7–3.1)	NA
51–65 years	Finland	9	11.1 (1)	NA	NA
	Germany	95	6.3 (6)	NA	NA
	Latvia	9	33.3 (3)	NA	NA
	Poland	40	27.5 (11)	2.1 (0.5–17.4)	2 (0.9–4.3)
	Russia	48	31.3 (15)	2.3 (0.9–6.1)	**2.6 (1.2–5.5)**
	Sweden	22	27.3 (6)	**7.0 (1.3–193.1)**	1.9 (0.6–4.8)
	All countries	223	18.8 (42)	**3.5 (1.9–7.5)**	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	20.0 (3)	2.7 (0.4–76.1)	0.9 (0.2–2.9)
	Germany[b]	DM	DM	DM	DM
	Latvia	12	0	NA	NA
	Poland	46	34.8 (16)	**4.0 (1.4–16.7)**	**2.3 (1.1–4.9)**
	Russia	80	23.8 (19)	2.0 (0.9–4.7)	1.1 (0.5–2.2)
	Sweden	21	9.5 (2)	0.9 (0.1–4.0)	0.4 (<0.1–1.3)
	All countries	174	23.0 (40)	**2.4 (1.4–4.3)**	NA
Hospitalisation 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	25.0 (1)	9.0 (0.3–122.8)	1 (<0.1–6.8)
	Poland	9	22.2 (2)	1.2 (0.1–4.9)	0.8 (0.1–3.2)
	Russia	44	34.1 (15)	**3.2 (1.4–7.2)**	2.3 (0.7–12.4)
	Sweden	2	0	NA	NA
	All countries	62	29.0 (18)	**2.4 (1.4–4.9)**	NA

OR, odds ratio; CI, confidence interval; NA, not applicable (not relevant or could not perform the analysis due zero cases in the comparison); DM, data missing; Ref., reference value used for calculation in a given category.
Statistically significant results are in bold text.
In the within-country analysis, each risk factor was investigated per country. In the between-countries analysis, each country was investigated for risk factors for each patient population/subpopulation.

[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 was missing results for antibiotic treatment and hospitalisation.

Table 4
Univariate logistic regression analysis of risk factors within and between partner countries for extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* outpatient urinary tract infection isolates.

Risk factor/subpopulation	Country	Total no. 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 (0.4–1.5)
	Latvia	58	0	NA	NA
	Poland	95	7.4 (7)	NA	0.8 (0.3–1.7)
	Russia	197	15.7 (31)	NA	2.8 (1.6–4.8)
	Sweden	83	7.2 (6)	NA	0.8 (0.3–1.8)
Age					
18–30 years	Finland	8	0	NA	NA
	Germany	61	4.9 (3)	Ref.	1.4 (0.3–5.5)
	Latvia	24	0	NA	NA
	Poland	16	6.3 (1)	Ref.	2.8 (0.1–12)
	Russia	58	5.2 (3)	Ref.	1.7 (0.3–6.6)
	Sweden	26	3.8 (1)	Ref.	1.4 (0.1–6.6)
	All countries	193	4.1 (8)	Ref.	NA
31–50 years	Finland	13	0	NA	NA
	Germany	73	9.6 (7)	1.9 (0.5–9.8)	1.2 (0.4–2.9)
	Latvia	24	0	NA	NA
	Poland	35	5.7 (2)	0.8 (0.1–20.4)	0.8 (0.1–2.5)
	Russia	73	13.7 (10)	2.6 (0.8–13.5)	2.4 (1.0–5.8)
	Sweden	33	9.1 (3)	2.0 (0.3–52.3)	1.3 (0.3–3.8)
	All countries	251	8.8 (22)	2.1 (1.0–5.4)	NA
51–65 years	Finland	9	0	NA	NA
	Germany	81	8.6 (7)	1.7 (0.5–8.8)	0.5 (0.2–1.2)
	Latvia	9	0	NA	NA
	Poland	44	9.1 (4)	1.1 (0.2–30.6)	0.7 (0.2–1.8)
	Russia	66	27.3 (18)	**6.0 (2.0–30.6)**	**4.8 (2.2–11.2)**
	Sweden	24	8.3 (2)	1.9 (0.2–50.9)	0.7 (0.1–2.4)
	All countries	233	13.3 (31)	**3.4 (1.6–8.5)**	NA
Antibiotic treatment during last 12 months					
No	Finland	15	0	NA	NA
	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 (0.7–93.2)	0.7 (0.2–1.7)
	Russia	103	22.3 (23)	**2.8 (1.3–7.4)**	**3.2 (1.5–8.4)**
	Sweden	23	8.7 (2)	1.3 (0.2–6.3)	0.6 (0.1–2.0)
	All countries	205	15.1 (31)	**3.0 (1.6–6.3)**	NA
Hospitalisation 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	10.0 (1)	1.9 (0.1–10.6)	0.3 (<0.1–1.6)
	Russia	68	35.3 (24)	**9.0 (3.9–25.3)**	**6.8 (1.6–182.0)**
	Sweden	2	0	NA	NA
	All countries	87	28.7 (25)	**7.4 (3.9–14.7)**	NA

OR, odds ratio; CI, confidence interval; NA, not applicable (analysis was not relevant or could not perform the analysis due zero cases in the comparison); DM, data missing; Ref., reference value used for calculation in a given category.
Statistically significant results are in bold text.
In the within-country analysis, each risk factor was investigated per country. In the between-countries analysis, each country was investigated for risk factors for each patient population/subpopulation.

[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 was missing results for antibiotic treatment and hospitalisation.

Table 5
Univariate logistic regression analysis of risk factors within and between partner countries for multidrug-resistant (MDR) *Escherichia coli* outpatient urinary tract infection isolates.

Risk factor/subpopulation	Country	Total no. of isolates	MDR *E. coli* [% (*n*)]	Within-country OR (95% CI)	Between-countries OR (95% CI)[a]
Total resistance					
MDR	Finland	30	10.0 (3)	NA	0.8 (0.2–2.1)
	Germany	284	7.0 (20)	NA	0.3 (0.2–0.6)
	Latvia	58	1.7 (1)	NA	0.1 (<0.1–0.5)
	Poland	95	18.9 (18)	NA	1.5 (0.8–2.6)
	Russia	197	26.9 (53)	NA	3.4 (2.2–5.2)
	Sweden	89	13.5 (12)	NA	1.0 (0.5–1.8)
Age					
18–30 years	Finland	8	0	NA	NA
	Germany	75	2.7 (2)	Ref.	0.3 (<0.1–1.1)
	Latvia	24	0	NA	NA
	Poland	16	12.5 (2)	Ref.	2.5 (0.3–9.4)
	Russia	58	13.8 (8)	Ref.	**3.6 (1.2–10.8)**
	Sweden	29	10.3 (3)	Ref.	1.9 (0.4–6.2)
	All countries	210	7.1 (15)	Ref.	NA
31–50 years	Finland	13	15.4 (2)	NA	NA
	Germany	105	5.7 (6)	1.9 (0.5–15.4)	**0.4 (0.1–0.9)**
	Latvia	24	0	NA	NA
	Poland	35	11.4 (4)	0.8 (0.2–7.1)	1.4 (0.4–3.8)
	Russia	73	23.3 (17)	1.8 (0.5–5.0)	**5.8 (2.6–13.7)**
	Sweden	35	5.7 (2)	0.6 (0.1–3.4)	0.7 (0.1–2.2)
	All countries	285	10.9 (31)	1.6 (0.8–3.1)	NA
51–65 years	Finland	9	11.1 (1)	NA	NA
	Germany	104	11.5 (12)	4.0 (1.1–31.2)	**0.3 (0.1–0.5)**
	Latvia	9	11.1 (1)	NA	NA
	Poland	44	27.3 (12)	2.2 (0.6–18.3)	1.4 (0.6–2.8)
	Russia	66	42.4 (28)	**4.4 (1.9–11.9)**	**3.9 (2.1–7.4)**
	Sweden	25	28.0 (7)	3.1 (0.8–17.3)	1.4 (0.5–3.4)
	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	14.0 (8)	Ref.	Ref.
	All countries	245	9.8 (24)	Ref.	NA
Yes	Finland	15	20.0 (3)	NA	NA
	Germany[b]	DM	DM	DM	DM
	Latvia	12	0	NA	NA
	Poland	52	28.8 (15)	**4.2 (1.3–21.7)**	1 (0.5–1.9)
	Russia	103	37.9 (39)	**3.8 (1.9–8.5)**	**2.3 (1.3–4.4)**
	Sweden	23	13.0 (3)	1 (0.2–3.6)	0.4 (0.1–1.1)
	All countries	205	29.3 (60)	**3.8 (2.3–6.5)**	NA
Hospitalisation 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	14.0 (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	30.0 (3)	2.3 (0.4–8.8)	0.6 (0.1–2.1)
	Russia	68	50.0 (34)	**5.7 (2.9–11.6)**	**4.7 (1.5–24.4)**
	Sweden	2	0	NA	NA
	All countries	87	42.5 (37)	5.0 (3.0–8.4)	NA

OR, odds ratio; CI, confidence interval; NA, not applicable (analysis was not relevant or could not perform the analysis due zero cases in the comparison); DM, data missing; Ref., reference value used for calculation in a given category.
Statistically significant results are in bold text.
In the within-country analysis, each risk factor was investigated per country. In the between-countries analysis, each country was investigated for risk factors for each patient population/subpopulation.

[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 was missing results for antibiotic treatment and hospitalisation.

In Finland, the national UTI guidelines allow prescription of antibiotics to be made over the phone following a structured interview for a woman suffering from acute cystitis. Therefore, difficulties were faced when recruiting study subjects and this was reflected in the number of samples collected. However, the AMR levels measured were in general <20%, including the upper range of the 95% CI, except for trimethoprim, SXT, ampicillin and ciprofloxacin. The resistance levels were in line with data collected on urine samples also representing complicated UTIs and bacteraemic *E. coli* isolates [20], except that no ESBL-producing *E. coli* were detected in the NoDARS study. The current 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 SXT should be taken into consideration during that process.

For Germany, the resistance rate was <20% for trimethoprim, SXT and ciprofloxacin (upper range of the 95% CIs were slightly above 20%) (Table 2). Resistance to ampicillin and AMC was >30%. The results are in line with other studies showing high resistance rates to ampicillin and amoxicillin and resistance rates of <20% against trimethoprim and 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 >20% for trimethoprim, SXT and ampicillin. In addition, Latvia had very low rates of combined resistance and no ESBL-producing isolates were identified, which could be due to the sample size. Compared with Latvian data on UTIs reported to the Global Antimicrobial Resistance Surveillance System (GLASS) [22], the NoDARS resistance levels are slightly lower for ampicillin, cefotaxime and SXT but the same for ciprofloxacin. Another study, however small in size, indicated that for uncomplicated UTI in an outpatient setting, nitrofurantoin or furazidin (a nitrofurantoin analogue) was mainly used [23]. All antibiotics are prescription-only drugs in Latvia.

In Poland, resistance rates were >20% for trimethoprim, SXT, ampicillin and ciprofloxacin. The 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 who had received antibiotics during the last 3 months, this should be taken into consideration when

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

Question	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 treatment						
Fosfomycin		–	Yes	Yes	Yes	
Furazidin		–		Yes	Yes	
Mecillinam	Yes	–	Yes			Yes
Nitrofurantoin	Yes	–	Yes	Yes	Yes	Yes
Nitroxoline		–	Yes			
Trimethoprim	Yes	–	Yes[a]	Yes		
SXT		–		Yes		
Recommended second-line treatment						
Amoxicillin	Yes	–				
AMC	Yes	–		Yes		
Cefadroxil	Yes	–				Yes
Cefalexin	Yes	–				
Cefixime		–			Yes	
Cefpodoxime proxetil		–	Yes			
Ceftibuten		–			Yes	
Ciprofloxacin	Yes	–	Yes	Yes	Yes	
Levofloxacin	Yes	–	Yes	Yes	Yes	
Norfloxacin		–	Yes			
Ofloxacin	Yes	–	Yes	Yes	Yes	
Trimethoprim		–				Yes[a]
SXT		–	Yes			
Availability of NoDARS antibiotics						
Ampicillin	Yes	Yes	Yes	Yes[b]	Yes	Yes
AMC	Yes	Yes	Yes	Yes	Yes	Yes
Cefuroxime	Yes	Yes	Yes	Yes	Yes	Yes
Ciprofloxacin	Yes	Yes	Yes	Yes	Yes	Yes
Fosfomycin	No[c]	No[c]	Yes	Yes[b]	Yes	No[d]
Nitrofurantoin	Yes	Yes	Yes	No[e]	Yes	Yes
Mecillinam	Yes	No[c]	Yes	No[c]	No[c]	Yes
Trimethoprim	Yes	Yes	Yes	Yes[b]	No[c]	Yes
SXT	Yes	Yes	Yes	Yes	Yes	Yes

STX, trimethoprim/sulfamethoxazole; AMC, amoxicillin/clavulanic acid; NoDARS, Northern Dimension Antibiotic Resistance Study.
[a] Only use if resistance of isolate is known.
[b] Not reimbursed.
[c] Not licensed.
[d] Fosfomycin is licenced but only for specific indications.
[e] Furazidin is a nitrofurantoin-like substance available without prescription.

evaluating the external validity of the AMR data for uncomplicated UTIs 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 health care. Nitrofurantoin use in the past or/and the current easy availability of furazidin may explain higher resistance to nitrofurantoin in Poland (6.1%) compared with other partner countries [0% for all, except for Russia (1.0%)]. High resistance of *E. coli* to nitrofurantoin (>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 to that reported in the current study (25.3%). The present results suggest that trimethoprim, SXT and ciprofloxacin included in the Polish treatment guidelines are unsuitable for empirical treatment.

For Russia, resistance rates >20% to ampicillin, trimethoprim and SXT in combination with 15.7% ESBL-producing *E. coli* isolates correlate with the general situation in Russia according to the national surveillance programme [25,26]. Russia had the highest resistance rate to ciprofloxacin (28.4%) among partner countries, which significantly limits the use of fluoroquinolones in the treatment of community-acquired UTI. This has already been taken into account in the current national UTI guidelines omitting this antibiotic class [27]. According to the questionnaires, Russia had the most patients hospitalised during the last 6 months (34.5%), which could also be a reason for the relatively high resistance rates of isolated *E. coli* since hospitalisation during the last 6 months was identified as a risk factor in Russia in this analysis.

The NoDARS results indicate that nitrofurantoin, fosfomycin and mecillinam were the most active oral antibiotics, with susceptibility rates of 98.8%, 98.7% and 95.9%, respectively. Taking into consideration that mecillinam is not available in Russia (Table 6), these results strongly support currently available national recommendations to use nitrofurantoin and fosfomycin as first-line antibiotics for the treatment of acute uncomplicated UTI [27].

In Sweden, resistance rates were >20% for trimethoprim, SXT and ampicillin. The results for nitrofurantoin, trimethoprim and ciprofloxacin were similar to data for complicated UTI from national surveillance [28]. The number of suspected ESBL-producing isolates was similar between NoDARS (5.8%) and national data from complicated UTI (5.5%) and bloodstream infection (7.8%) [28].

The Swedish first-line treatment recommendations for uncomplicated UTI were supported by the results of this study (Table 6). Sweden had one positive risk factor of older age (51–65 years) for patients with a UTI caused by ciprofloxacin-resistant *E. coli*. Although the 95% CI was broad (1.3–193.1), 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 partner countries was low, there might be limitations in the comparison of levels of resistance between certain countries. Also, samplings were mainly done regionally, which gives 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 observed [20,28]. Another possible limitation might be variations in collecting urine samples between countries with such dissimilar healthcare systems. However, the almost equal median and mean age of the patients confirms conformity of the population and the validity of the survey. Some patient had received antibiotics and been hospitalised (Table 1), which might have increased the overall AMR rate. As no multivariate analysis was performed, it is hard to draw conclusions regarding 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 varied significantly among partner countries suggesting continuation of surveillance monitoring and further local epidemiological studies, which are mandatory for guideline updating and correct empirical therapy.

Although variations exist, antibiotics with good susceptibility (nitrofurantoin, mecillinam and fosfomycin) were found in all partner countries supporting the usefulness of international recommendations. Between- and within-country analyses demonstrated risk factors for the prevalence of antimicrobial-resistant UTIs, providing more evidence to identify patient populations with potential treatment challenges.

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Competing interests

None declared.

Ethical approval

Ethical approval was obtained for Sweden [Etikprövningsnämnden Stockholm: 2015/1893-31/1], Finland [Ethics Committee, Hospital District of Southwest Finland: ETMK 158/1801/2015], Russia [Independent Ethics Committee of Smolensk State Medical University #184], Germany [Ethics Committee of Charité – Universitätsmedizin Berlin: EA2/008/15], Latvia [Ethics committee for Clinical Research at Pauls Stradins Clinical University Hospital: 040815–12E] and Poland [Bioethical Commission in IOMEH:1/2016].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jgar.2018.11.004.

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