1. Distributie en resistentieprofiel van geïsoleerde pathogenen bij vrouwen met een ongecompliceerde urineweginfectie in de eerstelijnszorg.
2. Verbeteren van de empirische therapiebegeleiding: Het filteren van laboratoriumgegevens ter verbetering van het toezicht op de resistentie van uropathogenen

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Masterproef 1

Abstract

Inleiding: In de eerstelijnszorg worden urineweginfecties (UWI's) doorgaans empirisch behandeld, op basis van de waarschijnlijke verwekkers en hun resistentieprofielen. Het doel van deze studie was om de huidige distributie en resistentie van uropathogenen te evalueren en te spiegelen aan de bestaande richtlijnen.

Methode: De distributie en resistentie werden geanalyseerd en vergeleken met gegevens uit drie eerdere onderzoeken die de afgelopen 25 jaar in België werden uitgevoerd. Tussen augustus 2020 en februari 2022 verzamelden 137 huisartsen urinestalen van volwassen vrouwelijke patiënten met cystitisklachten. De dipslide werd geënt en opgestuurd voor microbiologische analyse.

Resultaten: Van de 237 patiënten hadden 201 (85%) positieve kweekresultaten. *Escherichia coli* (74,6%) was het meest geïsoleerde uropathogeen, gevolgd door Staphylococcus saprophyticus (8%), Enterococcus faecalis (6,6%) en Klebsiella pneumoniae (3,3%), wat de resultaten van de onderzoeken uit 1995, 2005 en 2015 bevestigt. De gevoeligheid van *E. coli* in 2020 bleef 100% voor nitrofurantoïne en fosfomycine. Voor ampicilline was er een geleidelijke toename van resistentie, met een gevoeligheid van 53,5% in 2020. De gevoeligheidspercentages bedroegen 97,5% voor levofloxacine en 83,6% voor trimethoprim-

sulfamethoxazol. In tegenstelling tot eerdere onderzoeken werd pivmecillinam opgenomen in het onderzoek van 2020, met een gevoeligheid van 94,8%.

Conclusie: Over een periode van 25 jaar bleef de distributie en antimicrobiële gevoeligheid van uropathogenen geassocieerd met ongecompliceerde UWI's stabiel. Voor het eerst in België werd de gevoeligheid van *E. coli* voor pivmecillinam onderzocht, met als conclusie een goed resistentieprofiel. Dit suggereert dat pivmecillinam kan overwogen worden bij de behandeling van ongecompliceerde UWI’s.

Overview and resistance profiles of isolated pathogens in women with uncomplicated Urinary Tract Infection in primary care

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Introduction

Uncomplicated urinary tract infections (UTIs) are among the most prevalent infections encountered in general practice, with an estimated prevalence of 103.5 cases per 1,000 person-years among adult women (1). Diagnosis is based on clinical signs (e.g. dysuria, frequency, and urgency), often supported by urine dipstick testing for leukocyte esterase and nitrite (2). Empirical antibiotic treatment can be initiated without prior urine cultures (3).

Empirical treatment requires knowledge of the most common uropathogens and their antimicrobial susceptibilities (4). Existing data are often derived from retrospective susceptibility analyses of bacterial isolates obtained from urine cultures in regional microbiological laboratories (4). These results may be biased by the results of patients with complicated UTIs or associated risk factors. Therefore they may not accurately reflect the situation in uncomplicated UTIs encountered in primary care, potentially overestimating current bacterial resistance rates and leading clinicians to prescribe broader-spectrum antibiotics unnecessarily (4). To provide reliable recommendations, it is crucial to study causative organisms and their susceptibility patterns within a representative population (4).

In uncomplicated UTIs in Belgium, *Escherichia coli (E. coli)* is the most frequently isolated uropathogen (77.5% - 81.6%), followed by *Staphylococcus saprophyticus* (8% - 13.5%), *Enterococcus faecalis* (5.2%), and *Klebsiella pneumoniae* (3.3%) (4, 5). Nitrofurantoin, fosfomycin, trimethoprim-sulfamethoxazole (TMP-SMX) or pivmecillinam are recommended as empirical treatments for uncomplicated UTIs (4, 6).

Currently, pivmecillinam is only recommended in Scandinavian countries. In other European countries, it is not available or included in national guidelines (7). In Belgium, pivmecillinam has been available since 2020, but data on its use remain scarce.

Notably, pivmecillinam functions as a prodrug of mecillinam with its binding site on penicillin-binding protein 2 (PBP2) (8). Previous studies have consistently demonstrated stable resistance rates for pivmecillinam in *E. coli* induced UTIs, justifying its clinical use as a first-line empirical treatment (9).

This study aimed to assess the current antimicrobial susceptibility of uropathogens in non-pregnant adult women with uncomplicated UTIs in general practice. Additionally, we aimed to describe the evolution of susceptibility profiles by comparing our findings with data from previous observational studies conducted in the same geographic region (4).

Method

Study Population

From August 2020 to February 2022, 137 general practitioners (GPs) from 38 practices in the province of East Flanders and Antwerp (Belgium) participated. This study included female patients aged > 18 years who presented with dysuria, urgency and/or frequency. Exclusion criteria were symptoms lasting longer than seven days, predisposing factors (pregnancy, known urologic or nephrologic problems, diabetes mellitus, other immunocompromising diseases), recurrent UTI (more than three occurrences in the previous year), receiving antibiotics in the previous four weeks or obvious gynaecologic complaints (abnormal discharge, labial irritation, intermittent vaginal blood loss, or vaginal itch).

The geographical area and recruitment method were identical to those used in the 1995, 2005, and 2015 studies and most of the participating practices had previously contributed.

Finally, we sent preliminary reports and reminder emails to encourage each GP to include all eligible patients.

Collection of data

GPs completed a symptom questionnaire for each patient. All participants received oral and written information and provided informed consent.

After collecting a midstream urine sample, a dipslide (Uricult®, Aidian) was immediately inoculated, conforming to the manufacturer's instructions, and delivered to the Laboratory of

Medical Microbiology at Ghent University Hospital for incubation and microbiological analysis.

Study approval was obtained from the ethical committee of Ghent University Hospital (approval number EC UZG 2013/680).

Bacteriological analysis

Dipslides with MacConkey agar and CLED agar (Uricult®) were used for chairside inoculation of freshly voided urine, sent by post to the laboratory, and incubated overnight at 35°C in an ambient atmosphere and for another 24 h.

All colony types were identified using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) (Microflex LT, Bruker, Billerica, Massachusetts, USA). Quantitative data were obtained by matching the colony density with the model charts in the package insert according to the manufacturer's instructions (10).

The criteria for positivity of a urine culture were in accordance with the European Federation for Urinalysis (EFU) guidelines (11). The cut-off for significant bacteriuria in symptomatic UTI caused by primary uropathogens (*Escherichia coli* and *Staphylococcus saprophyticus*) was set at $\geq 10^3$ colony forming units (CFU)/mL in midstream urine specimens and at $\geq 10^4$ CFU/mL for secondary uropathogens (mainly other gram-negative rods and *Enterococcus* spp.). A second isolate was considered significant if it was identified as a primary or

secondary pathogen with bacterial counts of $\geq 10^4$ CFU/mL. Three organisms were identified as contaminants (12). Antibiotic susceptibility was tested using the Kirby– Bauer disk diffusion method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (12).

The EUCAST 2020 breakpoints for *E. coli* were identical to those of EUCAST 2014 for ampicillin, nitrofurantoin, amoxicillin-clavulanic acid, piperacillin-tazobactam, cefotaxime, ceftazidim, meropenem and pivmecillinam. For these antibiotics, the observed differences were solely due to real changes in the susceptibility data (12). For cefuroxime, levofloxacin, gentamicin, amikacin and tobramycin, the EUCAST 2020 breakpoints are stricter than those of EUCAST 2014. For TMP-SMX and TMP, the EUCAST 2020 breakpoints are less strict than those of EUCAST 2014 (12). For these antibiotics, the observed differences can also be attributed to these changes (12).

EUCAST 2020 and 2021 are different with respect to the lower breakpoints for tobramycin in 2021 (12). As there were no disk diffusion breakpoints available in EUCAST 2014 for fosfomycin, minimum inhibitory concentration (MIC) breakpoints were used in our 2015 study (12). In EUCAST 2020 and 2021, fosfomycin disk diffusion breakpoints were provided (12).

The susceptibility of *S. saprophyticus* and enterococci to fosfomycin was determined quantitatively as MICs using the Etest (bioMérieux, Marcy l'Etoile, France) (13).

The presence of ESBL in *E. coli* and other Enterobacteriaceae was detected with the disk approximation test (ceftazidime, ceftriaxone, and cefepime disks next to the amoxicillin–clavulanic acid disk, and the appearance of "ghost" zones after incubation).

Statistical analysis

SPSS Statistics 27 was used for statistical analysis. An X^2 test was performed to detect differences in uropathogen susceptibility and distribution between this study and those from 1995, 2005 and 2015 and between pre- and postmenopausal women. When the sample size in a cell was < 5, Fisher's exact test was used. A p-value less than 0,05 was considered significant.

Informed consent

All participants received oral and written information and provided verbal informed consent.

Results

Results of the 2020 study and comparison with the 2015, 2005 and 1995 surveys.

Characteristics of the four surveys

The characteristics of the four surveys were comparable (Table 1). However, some differences were noteworthy.

a) Postmenopausal women were not included in the 1995 survey.

b) In 1995 and 2005 NCCLS/CLSI breakpoints for susceptibility testing were used. The EUCAST 2014 and 2020 breakpoints were used in 2015 and 2020, respectively.

c) In 1995, 10^5 CFU/mL was used as the cut-off for a significant culture of *E. coli*; in the 2005 survey 10^3 CFU/mL was applied and in 2015 and 2020 the EFU criteria were used.

Table 1. Characteristics of the studies of 1995, 2005, 2015 and 2020.

	2020	2015	2005	1995
Study duration (months)	19	20	17	19
Number of samples	237	256	299	279
% positive samples (cut-off ≥105 CFU/mL)	62,00%	63,70%	65%	59%
% positive samples (EFU criteria)**	84,80%	79,30%	71,20%	NA***
Breakpoints used for susceptibility testing****	EUCAST 2020/2021	EUCAST 2014	CLSI 2004	NCCLS 1994
Age groups				
Premenopausal women (18–55 years)	161 (71,6%)*	188 (73,4%)	222 (83%)	279 (100%)
Postmenopausal women (>55 years)	64 (28,4%)*	68 (26,6%)	45 (17%)	0
Mean age (years)	44,1	42,6	39	34
Mean age of premenopausal women (years)	34,6	34	33	34
Mean age of postmenopausal women (years)	67,8	67	68	NA

*Percentage relative to 225 samples, where the date of birth is known. The date of birth is unknown for 12 out of the 237 samples.
**EFU: European Federation for Urinalysis.
***No data available for an updated interpretation with EFU criteria.
****EUCAST 2020/2021 breakpoints are similar, lower, or higher than the EUCAST 2014, CLSI 2004 and NCCLS 1994 breakpoints. More details are provided in the results section.

Distribution of uropathogens

Of the 237 enrolled patients, 201 (84.8 %) had a positive culture according to the EFU criteria. *E. coli* (74,6 %) was the most frequently isolated uropathogen, followed by *S. saprophyticus* (8%), *E. faecalis* (6,6 %) and *K. pneumoniae* (3,3 %) (Table 2). Among the urine samples, 12 contained a second uropathogen considered clinically significant. Compared with previous studies, the distribution of uropathogens remained largely unchanged.

Susceptibility pattern

The susceptibility of *E. coli* in 2020 was 100% for nitrofurantoin and fosfomycin, 97,5% for levofloxacin, 83,6% for TMP-SMX and 53,5% for ampicillin (Table 3). Regarding amoxicillin-clavulanic acid, validated breakpoints for both systemic and urinary use are available. In this case, only the systemic breakpoints were applied, resulting in a susceptibility rate of 91,8% for *E. coli.* Contrary to previous surveys, pivmecillinam was included in the 2020 survey with a susceptibility of 94,8% (Table 3). Susceptibility to second-line antibiotics was assessed. No substantial resistance was observed (Table 3).

Compared to the data from 1995, 2005, and 2015, the susceptibility rates of *E. coli* to nitrofurantoin and fosfomycin have remained stable (Table 3). However, resistance to ampicillin gradually increased until 2015, after which it has remained stable. In 2015, a non-significant increase in *E. coli* resistance to TMP and TMP-SMX was observed compared to

2005 and 1995. By 2020, susceptibility ratios had returned to previous levels, indicating that the observed trend did not persist, although ongoing monitoring remains important given that TMP-SMX is recommended as empirical treatment in elderly patients. (Table 3).

Comparison of pre- and postmenopausal women

In 2015 and 2020, there were no major differences in pathogen distribution in either age group, except for the presence of *S. saprophyticus*, which was found in one postmenopausal patient in 2020 and was completely absent in this population in 2015 (Table 4). In 2020, a statistically significant difference in the distribution of S. saprophyticus was found between premenopausal and postmenopausal women. A statistically significant difference in *E. coli* susceptibility to TMP was observed between premenopausal and postmenopausal women. Furthermore, no statistically significant differences in *E. coli* susceptibility to any other antibiotic were observed, which is consistent with the findings from 2015 (Table 5).

Table 2. Distribution of uropathogens in culture positive samples. All age groups included.

	2020 ($n = 213$)*	2015 ($n = 212$)	2005 ($n = 213$)	1995 ($n = 176$)
E. coli	159 (74,6%)	173 (81,6%)	171 (80,3%)	138 (78,4%)
S. saprophyticus	17 (8,0%)	17 (8%)	18 (8,5%)	16 (9,1%)
Enterococcus faecalis	14 (6,6%)	11 (5,2%)	1 (0,7%)	4 (2,3%)
Proteus spp.	2 (1%)	0	9 (4,2%)	7 (4%)
K. pneumoniae	7 (3,3%)	7 (3,3%)	6 (2,8%)	0
Other Gram-negative bacteria	12 (5,6%)	2 (1%)	6 (2,8%)	5 (2,8%)
Other Gram-positive bacteria	2 (1%)	2 (1%)	2 (0,7%)	4 (2,3%)

*Number of isolates detected. In twelve positive samples, two uropathogens were isolated.

Table 3. Susceptibility of *Escherichia coli*.

	2020 (*n* = 159)	2015 (*n* = 173)	2005 (*n* = 170)	1995 (*n* = 138)	p-value (2020 vs 2015)	p-value (2015 vs 1995)
Ampicillin	85 (53,5%)	96 (55,5%)	107 (62,9%)	101 (73,2%)	0,794	0,0013
Trimethoprim – sulfamethoxazole**	133 (83,6%)	132 (76,3%)	144 (84,7%)	115 (83,3%)	0,126	0,1275
Trimethoprim	123(80,4%) |6 ND*	132 (76,3%)	144 (84,7%)		-	-
Nitrofurantoin EUCAST (2014) breakpoint	159 (100%)	172 (99,4%)			1,0000	-
Nitrofurantoin CLSI/NCCLS breakpoint*			169 (99,4%)	137 (99,3%)	-	-
Cefuroxime	154(96,9%)	167 (96,5%)	) 167 (98,2%)		-	-
Fosfomycin	158 (99,4%)	173 (100%)	168 (98,8%)		0,4789	-
Levofloxacin**	155 (97,5%)	163 (94,2%)	168 (98,8%)	137 (99,3%)	0,176	0,0261
Amoxicillin – clavulanic acid Systemic breakpoint	146 (91,8%)	166 (96,0%)	148 (87,0%)		0,177	-
Amoxicillin – clavulanic acid Urinary breakpoint		169 (97,7%)			-	-
Gentamicin**	145 (96,0%) 8 ND	169 (97,7%)	169 (99,4%)		-	-
Temocillin	159 (100%)	172 (99,4%)			-	-
Amikacin	159 (100%)	173 (100%)			-	-
Piperacillin – tazobactam	155 (97,5%)	169 (97,7%)			-	-
Cefotaxime	155 (97,5%)	167 (96,5%)	-	-	-	-
Ceftazidime	158 (99,4%)	171 (98,8%)	-	-	-	-
Meropenem	159 (100%)	173 (100%)	-	-	-	-
Tobramycin	86(97,7%) |71 ND*	-	-	-	-	-
Pivmecillinam	145 (94,8%) |6 ND*	-	-	-	-	-

*No resistance determination was performed for this antibiotic in these samples (ND = not determined).

Table 4. Distribution of uropathogens in culture-positive samples according to age group.

	2020			2015	
	18-55J (*n* = 144)*	>55J (*n* = 58)*	p-value pre- vs. postmenopausal	18-55J (*n* = 153)	>55J (*n* = 59)
E. coli	101 (70,1%)	48 (82,8%)	0,0954	120 (78,4%)	53 (89,8%)
S. saprophyticus	16 (11,1%)	1 (1,7%)	0,0273	17 (11,1%)	0
Proteus spp.	1 (0,7%)	1 (1,7%)		0	0
Enterococcus faecalis	11 (7,6%)	3 (5,2%)	0,7610	8 (5,2%)	3 (5,1%)
Klebsiella pneumoniae	5 (3,5%)	1 (1,7%)		5 (3,3%)	2 (3,4%)
Other, Gram-negative	8 (5,6%)	4 (6,9%)		1 (0,7%)	1 (1,8%)
Other, Gram-positive	2 (1,4%)	0		2 (1,4%)	0

*The total number of samples is 202 instead of 213, which is due to the lack of a date of birth in the 11 samples.

Table 5. Antibiotic resistance of *E. coli* compared between premenopausal and postmenopausal women.

	2020			2015		
	Age 18–55 years (*n* = 92)	Age > 55 years (*n* = 41)	Pre- vs postmenopausal p-value	Age 18–55 years (*n* = 120)	Age > 55 years (*n* = 53)	Pre- vs postmenopausal p-value
Ampicillin	46 (50,0%)	26(63,4%)		66 (55%)	30 (56,6%)	
TMP-SMX	75 (81,5%)	38 (92,7%)	0,119	89 (74,2%)	43 (81,1%)	0,3206
TMP	68 (77,3%)|4 ND*	36 (92,3%)|2 ND*	0,0477	89 (74,2%)	43 (81,1%)	
Nitrofurantoin	92(100%)	41 (100%)		119 (99,2%)	53 (100%)	
Cefuroxime	90 (97,8%)	38 (92,7%)	0,170	117 (97,5%)	50 (94,3%)	
Fosfomycin	92 (100%)	41(100%)		120 (100%)	53 (100%)	
Levofloxacin	89 (96,7%)	40 (97,6%)	1,000	115 (95,8%)	48 (90,6%)	0,1776
Amoxicillin-clavulanic acid**	83 (90,2%)	38(92,7%)	0,754	115 (95,8%)	51 (96,2%)	1,000
Gentamicin	83 (94,3%)|4 ND*	36 (97,3%)|4 ND*		116 (96,7%)	53 (100%)	
Temocillin	92 (100%)	41(100%)		119 (99,2%)	53 (100%)	
Amikacin	92 (100%)	41 (100%)		120 (100%)	53 (100%)	
Piperacillin-tazobactam	90(97,8%)	40 (97,6%)		119 (99,2%)	50 (94,3%)	
Cefotaxime	90 (97,8%)	40 (95,1%)		118 (98,3%)	49 (92,5%)	
Ceftazidime	92 (100%)	40 (95,1%)		120 (100%)	51 (96,2%)	
Meropenem	92 (100%)	41(100%)		120 (100%)	53 (100%)	
Tobramycine	45 (97,8%)|46 ND*	20 (95,2%)|20 ND*		-	-	
Pivmecillinam	80 (92,0%)|5 ND*	41 (100%)	0,096	-	-	

*No resistance testing was performed for this antibiotic on any of samples. (ND = not determined).
**Systemic breakpoints.

Discussion

This is the latest in a series of four observational studies on uropathogen susceptibility in women with uncomplicated UTIs in primary care. All studies were conducted within the same Belgian region using consistent methodologies across the surveys. These studies' similar approaches and regional characteristics enable a reliable comparison of results (4). However, exclusive data collection from one region limits the generalizability to other areas.

The majority of the recruited GPs were from training practices, which may have contributed to more restrictive antibiotic prescriptions. However, this was similarly observed in the previous three studies, again reducing potential bias.

Over a 25-year period, the distribution and susceptibility of uropathogens to uncomplicated UTIs remained stable. *E. coli* susceptibility to nitrofurantoin and fosfomycin remained 100%. No significant decline in susceptibility was observed for other commonly used antibiotics. There was no difference in the distribution of uropathogens between pre- and post-menopausal women, which is consistent with the results of previous studies, except for the prevalence of *S. saprophyticus*, which was predominantly found in premenopausal women.

The *E. coli* susceptibility observed in our study aligns with the 2009 ARESC study, a surveillance study across nine European countries and Brazil. This study reported high susceptibility rates for fosfomycin (98%), nitrofurantoin (95.9%), and quinolones (91.8%),

whereas susceptibility to ampicillin was low (45%) (14). The susceptibility to TMP-SMX was 70.5%, with rates exceeding 80% in three countries (14).

A more recent Northern Dimension Antibiotic Resistance study (NoDARS), which examined antimicrobial resistance in Finland, Germany, Latvia, Poland, Russia and Sweden, showed an *E. coli* susceptibility rate of 98,8% for nitrofurantoin, 98,7% for fosfomycin and 95,9% for pivmecillinam, which is similar to our findings (15). A recent Dutch study by Van Driel et al. (2019) reported an *E. coli* susceptibility rate of 99% to nitrofurantoïn and Fosfomycin (16). The Swiss study by Plate et al. (2019) found similar results with a susceptibility rate of 99,4% for fosfomycin, 99,48% for nitrofurantoin and 85,66 for TMP-SMX, although this varied per region (17).

The high susceptibility of *E. coli* to nitrofurantoin and fosfomycin is both noteworthy and reassuring, given their frequent use as first-line empirical treatments.

Nitrofurantoin exerts antimicrobial effects through multiple metabolic pathways that disrupt the cellular integrity (18). It interferes with bacterial protein synthesis and the ribosomal machinery (18). Additionally, nitrofurantoin disrupts the Krebs cycle by inhibiting key enzymes and compromising energy production. It also contributes to impairment of cell wall synthesis (18). This multifaceted mechanism of action, combined with selective and limited clinical use, may contribute to the relatively low incidence of resistance development (18). Another possible reason for this could be the relatively low total consumption of these

antibiotics, as they are only prescribed for uncomplicated UTIs, unlike other antibiotics with broader indications.

Although not statistically significant, a slight downward trend in ampicillin susceptibility was observed, potentially reflecting the broad use of beta-lactam antibiotics. Ongoing monitoring is recommended.

The susceptibility of *E. coli* to TMP-SMX increased from 76.3% to 83.6% compared to the study by Heytens et al., although this difference was not statistically significant (4). The explanation for this observation is the use of EUCAST 2020 and 2021 breakpoints. The use of these breakpoints may result in higher susceptibility to TMP-SMX and TMP in *E. coli (12)*.

Although quinolone susceptibility to *E. coli* remains high, they are not recommended as first-line empirical therapy for uncomplicated urinary tract infections because of their broad-spectrum activity and potential side effects including gastrointestinal disorders, arthralgia and QT prolongation (6, 19). The widespread use of quinolones for uncomplicated UTIs could lead to increased resistance, reducing their efficacy in more severe infections requiring tissue penetration. Therefore, quinolones are reserved for more complicated infections such as pyelonephritis or prostatitis (6).

Amoxicillin-clavulanic acid is not the first-line treatment because of its broad-spectrum activity and potential side effects. *E. coli* susceptibility in our study remained high. Similar to

quinolones, amoxicillin-clavulanic acid is reserved for complicated or polymicrobial infections. A statistically non-significant decrease in susceptibility was observed from 96% in 2015 to 91.8% currently (4). However, this pertains to the systemic breakpoint of amoxicillin-clavulanic acid. Although urinary breakpoints were discussed in a previous study, they were not addressed in this study.

To our knowledge, this is the first study in Belgium to examine *E. coli* susceptibility to pivmecillinam. Pivmecillinam is a prodrug of mecillinam that has a binding site on PBP2. PBPs are key players in peptidoglycan biosynthesis (8). Despite being available on the Belgian market between 2020 and 2024, the molecule has not yet been incorporated into national guidelines for the management of urinary tract infections or for any other clinical indications (6). If pivmecillinam were to be included in the national guidelines in Belgium, this could encourage pharmaceutical companies to improve its availability and ensure that it becomes accessible on the Belgian market again. In several European countries, particularly those in Scandinavia, pivmecillinam is recommended as an empirical treatment for uncomplicated UTIs. Clinical guidelines from Denmark, Sweden, Norway and Finland include pivmecillinam as the first-line therapeutic option (20-23). Similarly, the German and British guidelines acknowledge the use of pivmecillinam for uncomplicated UTIs, although not as the first choice (3, 24). In this study, *E. coli* susceptibility was 94.8% compared to a 4,1% resistance rate in the NODARS study (15).

Pivmecillinam was not prescribed in this study. Because its role in urinary tract infection management has not yet been clearly defined, pivmecillinam remains relatively unknown among general practitioners and is presently unavailable in Belgium. In addition, the cost of treatment with pivmecillinam (€14.14) exceeds that of nitrofurantoin (€10.92) and fosfomycin (€10.19)(25). Because of their proven efficacy, favorable safety profiles, and the aim to minimize antimicrobial resistance, nitrofurantoin and fosfomycin remain the first-line treatments for uncomplicated urinary tract infections(3, 6, 26).However, pivmecillinam may be considered an alternative for specific clinical indications. Unfortunately, pivmecillinam has not been available in Belgium since January 2024 for reasons that have not been clearly disclosed(27).

Currently, TMP is, according to Belgian guidelines, recommended as the first-choice treatment in elderly patients and those with chronic kidney disease (CKD), while pivmecillinam seems to be a better alternative due to a higher susceptibility rate (6). During the final weeks of pregnancy fosfomycin is recommended instead of nitrofurantoin, because of the risk of hemolytic anemia in neonates(6). Pivmecillinam should also be considered for this indication.

Approximately 8–10% of uncomplicated urinary tract infections in women are attributed to *S. saprophyticus* in community settings(28)**.** Although older studies reported high levels of resistance of *S. saprophyticus* to fosfomycin (29, 30)**,** more recent large-scale susceptibility studies have not provided clear or up-to-date quantitative data confirming fosfomycin resistance in this species. A limitation of the present study is that the susceptibility of *S.*

saprophyticus to fosfomycin was not assessed. Given this uncertainty and the non-negligible prevalence of *S. saprophyticus*, a note of caution is warranted: empirical fosfomycin therapy may not reliably cover this pathogen, and local susceptibility data or alternative agents (e.g., nitrofurantoin, trimethoprim/sulfamethoxazole) should be considered in settings where *S. saprophyticus* is common.

The data were primarily collected around Ghent, East Flanders, which is consistent with the findings of previous studies. Caution is needed when generalizing these findings to the broader population of Belgium. Further research in other regions is needed to validate these findings. The GPs involved mostly worked in teaching practices, which may have influenced a more constrained antibiotic prescription approach. However, this is unlikely to introduce significant bias, as similar practices have been included in prior studies.

Conclusion

Over a 25-year period, the distribution and antimicrobial susceptibility of uropathogens associated with uncomplicated UTIs has remained stable. The *E. coli* susceptibility to nitrofurantoin and fosfomycin remained 100%. For the first time, in Belgium, we assessed pivmecillinam and found an *E. coli* susceptibility rate of 94.8%. This suggests that pivmecillinam could be considered a potential alternative for the empirical treatment of

uncomplicated UTIs, particularly in the elderly, individuals with CKD, or patients in the final weeks of pregnancy.

Author contribution statement

Loic Vanderpoorten, Siebe Vandevelde, Lien De Corte, Jasper Holvoet, Laura Vandevelde, Camille Thys, Eline Thyssen, Lieselot Veekens, Fatou Touré, Jerina Boelens, and Stefan Heytens were all involved in the conception and design, analysis, interpretation of the data, drafting of the paper, and critical revision of the manuscript for intellectual content. All authors were involved in the final approval of the version to be published and all authors agree to be accountable for all aspects of the work.

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Disclosure of interests

There were no conflicts of interest in this study.

References

1. Lelie-van der Zande R, Bouvy M, Teichert M. Adherence to guideline recommendations for urinary tract infections in adult women: a cross-sectional study. Prim Health Care Res Dev. 2021;22:e11.
2. Kranz J, Schmidt S, Lebert C, Schneidewind L, Mandraka F, Kunze M, et al. The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients: Part 1. Urol Int. 2018;100(3):263–70.
3. NICE Guideline - Urinary tract infection (lower): antimicrobial prescribing 2018 [updated 2024. Available from: https://www.nice.org.uk/guidance/ng109/resources/urinary-tract-infection-lower-antimicrobial-prescribing-pdf-66141546350533.
4. Heytens S, Boelens J, Claeys G, DeSutter A, Christiaens T. Uropathogen distribution and antimicrobial susceptibility in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20-year surveillance. Eur J Clin Microbiol Infect Dis. 2017;36(1):105–13.
5. De Backer D, Christiaens T, Heytens S, De Sutter A, Stobberingh EE, Verschraegen G. Evolution of bacterial susceptibility pattern of Escherichia coli in uncomplicated urinary tract infections in a country with high antibiotic consumption: a comparison of two surveys with a 10 year interval. J Antimicrob Chemother. 2008;62(2):364–8.
6. BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulate praktijk - 2022: BCFI; 2022. Available from: https://www.bcfi.be/nl/chapters/12?frag=8000010.
7. Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. J Antimicrob Chemother. 2014;69(2):303–8.
8. Salleh MZ, Banga Singh KK, Deris ZZ. Structural Insights into Substrate Binding and Antibiotic Inhibition of Enterobacterial Penicillin-Binding Protein 6. Life (Basel). 2022;12(7).
9. Bollestad M, Grude N, Solhaug S, Raffelsberger N, Handal N, Nilsen HS, et al. Clinical and bacteriological efficacy of pivmecillinam treatment for uncomplicated urinary tract infections caused by ESBL-producing Escherichia coli: a prospective, multicentre, observational cohort study. J Antimicrob Chemother. 2018;73(9):2503–9.
10. Clark AE, Kaleta EJ, Arora A, Wolk DM. Matrix-assisted laser desorption ionization-time of flight mass spectrometry: a fundamental shift in the routine practice of clinical microbiology. Clin Microbiol Rev. 2013;26(3):547–603.
11. Aspevall O, Hallander H, Gant V, Kouri T. European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. Clin Microbiol Infect. 2001;7(4):173–8.
12. European Committee on Antimicrobial Susceptibility Testing (EUCAST) - Clinical breakpoints 2024 [updated 2024. Available from: https://www.eucast.org/clinical_breakpoints.
13. López-Cerero L, de Cueto M, Díaz-Guerrero MA, Morillo C, Pascual A. Evaluation of the Etest method for fosfomycin susceptibility of ESBL-producing Klebsiella pneumoniae. J Antimicrob Chemother. 2007;59(4):810–2.
14. Schito GC, Naber KG, Botto H, Palou J, Mazzei T, Gualco L, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents. 2009;34(5):407–13.
15. Ny S, Edquist P, Dumpis U, Gröndahl-Yli-Hannuksela K, Hermes J, Kling AM, et al. Antimicrobial resistance of Escherichia coli isolates from outpatient urinary tract infections in women in six European countries including Russia. J Glob Antimicrob Resist. 2019;17:25–34.
16. van Driel AA, Notermans DW, Meima A, Mulder M, Donker GA, Stobberingh EE, et al. Antibiotic resistance of Escherichia coli isolated from uncomplicated UTI in general practice patients over a 10-year period. Eur J Clin Microbiol Infect Dis. 2019;38(11):2151–8.

17. Plate A, Kronenberg A, Risch M, Mueller Y, Di Gangi S, Rosemann T, et al. Treatment of urinary tract infections in Swiss primary care: quality and determinants of antibiotic prescribing. BMC Fam Pract. 2020;21(1):125.
18. Mahdizade Ari M, Dashtbin S, Ghasemi F, Shahroodian S, Kiani P, Bafandeh E, et al. Nitrofurantoin: properties and potential in treatment of urinary tract infection: a narrative review. Front Cell Infect Microbiol. 2023;13:1148603.
19. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103–20.
20. Holm A, Cordoba G, Aabenhus R. Prescription of antibiotics for urinary tract infection in general practice in Denmark. Scand J Prim Health Care. 2019;37(1):83–9.
21. Läkemedelsbehandling av urinvägsinfektioner i öppenvård – behandlingsrekommendation 2017. Available from: https://www.lakemedelsverket.se/48d71b/globalassets/dokument/behandling-och-forskrivning/behandlingsrekommendationer/behandlingsrekommendation/behandlingsrekommendation-lakemedel-urinvagsinfektioner.pdf.
22. Akutt cystitt hos sykehjemspasienter 2024 [updated August 2024. Available from: https://antibiotikaiallmennpraksis.no/index.php?action=topic&item=fb529ac1f41e9235886e.
23. Urinary tract infections 2024. Available from: https://www.kaypahoito.fi/hoi10050.
24. S3-Leitlinie Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei Erwachsenen (HWI) 2010 [updated 2024. Available from: https://register.awmf.org/assets/guidelines/043-044l_S3_Epidemiologie-Diagnostik-Therapie-Praevention-Management-Harnwegsinfektione-Erwachsene-HWI_2024-09.pdf.
25. BCFI: prices 2025. Available from: https://www.bcfi.be/nl/chapters/12?frag=10264&trade_family=11312.
26. NHG-standaarden: Urineweginfecties 2025. Available from: https://richtlijnen.nhg.org/standaarden/urineweginfecties#volledige-tekst-tabelh1.
27. BCFI: Onderbrekingen van commercialisatie (langdurige onbeschikbaarheden) 2024. Available from: https://www.bcfi.be/nl/articles/query?number=F51N02H#piv.
28. SCIENSANO: Surveillance of Antimicrobial Resistance in Primary Care – Urinary Tract Infections RESULTS 2024 2024. Available from: https://www.sciensano.be/sites/default/files/report_sarpric-uti.pdf?utm_source=chatgpt.com.
29. Loulergue J, Pinon G, Laudat P, Audurier A. [Fosfomycin resistance in Staphylococcus saprophyticus and other species of coagulase-negative staphylococci]. Ann Microbiol (Paris). 1984;135a(2):239–47.
30. Orden-Martínez B, Martínez-Ruiz R, Millán-Pérez R. [What are we learning about Staphylococcus saprophyticus?]. Enferm Infecc Microbiol Clin. 2008;26(8):495–9.

Masterproef 2

Abstract

Inleiding

Ongecompliceerde urineweginfecties (UWI's) worden in de eerste lijn meestal empirisch behandeld, waarbij richtlijnen sterk steunen op laboratoriumdata die vaak afkomstig zijn van geselecteerde (meer complexe) patiëntengroepen met risicofactoren en gecompliceerde urineweginfecties. Dit kan leiden tot een vertekend beeld van uropathogenen en hun resistentiepatronen in de algemene populatie. Actieve surveillance door middel van observationele studies bieden een oplossing, maar zijn duur en arbeidsintensief. Deze studie onderzocht of het toepassen van een filter op bestaande laboratoriumdatabases kan resulteren in gegevens die beter representatief zijn voor ongecompliceerde UWI's in de eerste lijn.

Methodologie

Een observationele studie bij 237 vrouwen met UWI-symptomen in Vlaanderen werd vergeleken met zowel ongefilterde als gefilterde laboratoriumdata van drie klinische laboratoria. Filtering gebeurde op basis van criteria zoals geslacht, leeftijd, afwezigheid van complicerende factoren en kenmerken van positieve urinestalen. Verder werd er ook maar één staal per patiënt per jaar geïncludeerd.

Resultaten

Resultaten tonen dat ongefilterde laboratoriumdata significant verschillen van de observationele gegevens. Na filtering werd de verdeling van uropathogenen, vooral *E. coli*, en de antibioticasusceptibiliteit vergelijkbaar met de observationele studie. Voor eerstelijnsantibiotica zoals nitrofurantoïne, fosfomycine en cotrimoxazol werden minder significante verschillen gevonden tussen gefilterde data en de observationele stalen.

Conclusie

In de praktijk baseren richtlijnen zich vaak op laboratoriumdata waarbij stalen van gecompliceerde urineweginfecties oververtegenwoordigd zijn. Dit moet in rekening gebracht worden bij de interpretatie van de gegevens voor het gebruik in richtlijnen voor de eerste lijn. In deze context kan een filterstrategie dienen als een doeltreffende aanpak.

"Improving Empirical Therapy Guidance: Filtering Laboratory Data to Enhance Surveillance of Uropathogen Resistance"

Vandevelde S, Vanderpoorten L, Van den Abeele A, Nuytten H, Claeys G, Christiaens T, De Sutter A, Coppens A, Overmeire Y, Depourcq G, Gehesquiere B, Windels C, Thys C, Thyssen E, Veekens L,Boelens J, Heytens S

Introduction

Uncomplicated lower urinary tract infections (UTIs) are among the most common infections encountered in primary care and are frequently managed with antibiotic therapy. (1, 2) Diagnosis is typically based on clinical presentation. Symptoms are dysuria, increased urinary frequency, and urgency. These clinical findings are often supplemented with urine dipstick testing. A positive nitrite result suggests a high likelihood of a bacterial UTI, while negative results for both nitrite and leukocyte esterase significantly reduce the probability of infection. (2, 3) Antibiotic treatment is commonly initiated empirically, often prior to microbiological confirmation. (1, 2, 3)

In uncomplicated UTI's, *Escherichia coli* (*E. coli*) is the predominant uropathogen, accounting for approximately 81.6% of isolates. Other commonly identified pathogens include *Staphylococcus saprophyticus* (8.0%), *Enterococcus faecalis* (5.2%), and *Klebsiella pneumoniae* (3.3%). (1, 4) Current clinical guidelines recommend empirical treatment with nitrofurantoin, fosfomycin, cotrimoxazole or pivmecillinam, based on local antimicrobial susceptibility patterns and individual patient factors. (1, 2, 3)

Development of the current guidelines

In order to establish guidelines for the empirical treatment of urinary tract infections (UTIs), it is essential to understand which uropathogens are prevalent and to determine their antimicrobial susceptibility profiles. (4) Currently, such microbiological data are primarily obtained from large clinical laboratories, many of which are affiliated with hospitals. However, the urine samples processed in these laboratories often originate from a selected patient population, typically characterized by risk factors, recurrent infections, or complicated UTIs.(5, 6, 8, 9, 10) Conclusions drawn from these data are frequently extrapolated to the primary care setting, despite the legitimate concern as to whether these findings are truly representative of the broader community-dwelling population. (5-10)

To address this discrepancy and develop evidence-based guidelines for empirical UTI treatment in primary care, active surveillance through observational studies is necessary.(6-8) Nevertheless, such studies are resource-intensive, both in terms of labor and cost.(9) Furthermore, given the dynamic nature of antimicrobial resistance, continuous surveillance would ideally be required to ensure up-to-date data.

Alternative methods

This has prompted a search for alternative methods to obtain reliable information on resistance patterns in the primary care population, without the need for continuous active surveillance. One potential approach involves applying specific filters to existing laboratory databases, thereby enabling the identification and selection of urine samples that are more representative of the primary care population. (7, 8, 10)

Method

Study population

Between August 2020 and February 2022, a total of 237 female patients were enrolled in the study through general practitioners in the Flanders region of Belgium. Eligible participants were women aged 18 years or older presenting with symptoms of dysuria, urinary urgency, and/or increased urinary frequency.

Exclusion criteria included: symptom duration exceeding seven days, current pregnancy, known predisposing conditions such as nephrological or urological disorders, diabetes mellitus, or immunocompromising diseases, recurrent UTIs (defined as more than three episodes within the past year), antibiotic use within the preceding four weeks or the presence of gynecological symptoms (e.g., abnormal vaginal discharge, labial irritation, intermittent vaginal bleeding, or vaginal pruritus).

Collection of data

For each enrolled patient, general practitioners completed a standardized symptom questionnaire. All participants received both oral and written information regarding the study and provided informed consent prior to inclusion.

Following collection of a midstream urine sample, a dipslide (Uricult®, Orion Diagnostica, Espoo, Finland) was inoculated in accordance with the manufacturer's instructions. The samples were then transported to the Laboratory of Medical Microbiology at Ghent University Hospital for incubation and microbiological analysis.

The study protocol was approved by the Ethics Committee of Ghent University Hospital (approval number: BC-07306).

Bacteriological analysis

The dipslides were incubated overnight at 35°C in ambient atmosphere followed by an additional 24-hour incubation. All colony types were identified using matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany). (11) Quantitative data were collected by matching the colony density with the model charts in the package insert, following the manufacturer's instruction. Antibiotic susceptibility was tested using the Kirby-Bauer disk diffusion method, in accordance with the guidelines established by the European Committee of Antimicrobial Susceptibility Testing (EUCAST) guidelines. (12)

Data Laboratories

Participating laboratories

Three clinical laboratories (AML, Labo Nuytinck and Labo ASZ) were requested to retrospectively apply a predefined filter protocol to microbiological data from urine samples in their data base collected between August 2020 and December 2021 (Table 1). In addition to the filtered data, the raw, unprocessed datasets were also provided for analysis. All participating laboratories assessed antimicrobial susceptibility in accordance with the EUCAST guidelines. (12)

Filter protocol

A filter protocol was developed to increase the likelihood of including urine samples from ambulatory women with uncomplicated UTIs. Inclusion criteria required that the patient was female and aged over 18 years. A urine sample was considered positive if pyuria was present, the bacterial count exceeded $>10^3$ colony-forming units per milliliter (CFU/mL) and either a single uropathogen was isolated or a clearly dominant uropathogen was identified (i.e.

absence of mixed flora). In the hospital-affiliated laboratories, the criteria of the European Federation for Urine analysis (EFU) were applied to define a positive urine sample. Samples originating from hospital patients or residents of long-term care facilities were excluded from analysis. Additionally, only one urine sample per patient per year was included (Table 1).

Table 1: Overview of setting and inclusion criteria

	Observational study	Labo AML	Labo Nuytinck	ASZ
Region	Antwerp, East- and West Flanders	Antwerp Ardooie (West Flanders)	Bruges (West Flanders) Ghent (East Flanders)	Aalst (East Flanders)
Setting	First line	Ambulant patients		
Selected patients	Women >= 18 years old Uncomplicated urinary tract infections	Women >= 18 years old Not more than one sample per year per patient Not from nursing homes or institutionalized patients Not from specialists, but from general practitioners		
Positive culture	EFU criteria *E. coli* >10^3 CFU/mL	EFU criteria *E. coli* >10^3 CFU/ mL + pyuria according to cut-off value of the lab	EFU criteria *E. coli* >10^3 CFU/ mL + pyuria according to cut-off value of the lab	EFU criteria *E. coli* >10^3 CFU/ mL + pyuria according to cut-off value of the lab
N	237	7915	7392	2547
Breakpoint criteria	EUCAST 2020/2021	EUCAST 2020	EUCAST 2020	EUCAST 2020

Labo AML: Labo Algemeen Medisch Labo

ASZ Aalst: Algemeen Stedelijk ziekenhuis Aalst

EFU: European Federation for Urine analysis

CFU: colony-forming units

N: Sample size

EUCAST: European Committee on Antimicrobial Susceptibility Testing

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 28. To assess differences in antimicrobial susceptibility between the observation surveillance study and laboratory data set, a X^2 test was performed. When cell counts were below five, Fisher's exact test was used, except in the comparison between the observational study and the unfiltered laboratory data. Due to the large sample size in this comparison, Fisher's exact test was not feasible, and a X^2 test with Yates correction was applied instead. A p-value less than 0,05 was considered significant.

Results

Observational surveillance study

Over a 19- month period, a total of 237 female patients with symptoms suggestive of a UWI were enrolled. The participants aged from 18 to 88 years, with a mean age of 44.1 years old. Among them161 (71,6%) were premenopausal, while 64 (28,4%) were postmenopausal (>55 years old). Based on the standard bacterial count criterion (>10^3 CFU/mL), 62% of

participants were diagnosed with a UTI. When applying the EFU criteria, 84,8% met the threshold for UTI diagnosis (Table 2).

Among the urine samples collected from participants, *E. coli* was the most frequently isolated uropathogen (74,6%), followed by *S. saprophyticus* (8,0%), *Enterococcus* spp. (6,6%) and *Klebsiella* spp. (3,3%) (Table 3). *E. coli* demonstrated high susceptibility to commonly prescribed antibiotics, including nitrofurantoin and fosfomycin (Table 9, 11).

Table 2: Characteristics observational surveillance study

Characteristics of the study	
Duration of the study (months)	19
Number of samples	237
% positive samples (>10^5CFU/mL)	62,0
% positive samples (EFU criteria)	84,8
Breakpoint criteria	EUCAST 2020/2021
Age groups*	
Premenopausal (18-55j)	161 (71.6%)
Postmenopausal (>55j)	64 (28.4%)
Mean age (years)	44.1
Mean age of premenopausal women (years)	34.6
Mean age of postmenopausal women (years)	67.8

* For 12 of the 237 samples the date of birth is unknown.

CFU: colony-forming units

EFU: European Federation for Urine analysis

Table 3: Distribution of uropathogens in the observational study

	Observational study N=213	
E. coli	159	74.6%
S. saprophyticus	17	8.0%
Klebsiella spp.	7	3,3%
Enterococcus spp.	14	6,6%
Enterobacter spp.	4	1,9%
S. aureus (*Staphylococcus aureus*)	0	0%
S. agalactiae (*Streptococcus agalactiae*)	1	0.5%
Proteus Mirabilis	2	0.9%
Other	9	4.2%

Unprocessed laboratory data

Urine samples were collected by participating laboratories (ASZ, Labo Nuytinck and ASZ) between August 2020 and December 2021. A total of 54 764 samples were obtained, distributed as follows: 19 472 samples by AML, 14 608 by Labo Nuytinck and 20 684 by ASZ. 75,1% of the samples collected by ASZ originated from female patients and 24,7 from male patients. At Labo Nuytinck, 76,4% of the samples were from females and 23,6% from males. Similarly, in the AML laboratory, 78,9% of the samples were from female patients and 21,1% from male patients (Table 4).

Table 4: Participant characteristics raw data

	AML N=19472		Labo Nuytinck N=14608		Labo ASZ N=20684	
Sex	Man	Woman	Man	Woman	Man	Woman
Total (n, %)	4103 * (21,1%)	15363 * (78,9%)	3424** (23,4%)	11181** (76,5%)	5110*** (24,7%)	15538 *** (75,1%)
<18 year (x, % of total)	4 (0,1%)	73 (0,5%)	81 (23,7%)	429 (3,8%)	117 (2,3%)	568 (3,7%)
18-54 (x, % of total)	754 (18,4%)	5134 (33,4%)	373 (10,9%)	2619 (23,4%)	490 (9,6%)	2954 (19,0%)
> 54 (x, % of total)	3345 (81,5%)	10156 (66,1%)	2970 (86,7%)	8133 (72,7%)	4503 (88,1%)	12016 (77,3%)

* The gender is unknown for 6 samples.

** The gender is unknown for 3 samples.

*** The gender is unknown for 36 samples.

Across all participating laboratories, *E. coli* was the most frequently isolated uropathogen, accounting for 66,6% of isolates at AML, 68,2% at Labo Nuytinck and 55,3% at ASZ. *Klebsiella* spp. (11,1%) emerged as the second most identified uropathogen, surpassing *S. saprophyticus* (1,7%) (Table 5).

Table 5: Distribution of uropathogens in raw laboratory data

	AML N=19472		Labo Nuytinck N=14608		Labo ASZ N= 20684	
E. coli	12963	66.6%	9960	68,2%	11432	55,3%
S. saprophyticus	177	0.9%	266	1.8%	356	1.7%
Klebsiella spp.	1850	9.5%	1491	10.2%	2304	11.1%
Enterococcus spp.	1313	6.7%	570	3.9%	2156	10.4%
Enterobacter spp.	357	1.8%	172	1,2%	638	3.1%
S. aureus	121	0.6%	88	0.6%	199	1.9%
S. agalactiae	389	2.0%	171	1.2%	50	0.2%
P. mirabilis	763	3.9%	860	5.9%	1304	6.4%
Other	1539	7.9%	1030	7.1%	2245	10.9%

Filtered laboratory data

After filter application, as described in the method section, there was an inclusion of 7915 samples at AML, 7392 samples at Labo Nuytinck and 2547 samples at ASZ. In total, results from a group of 6065 premenopausal and 11789 postmenopausal women were included (Table 6).

Table 6: Participant characteristics: filtered data

	AML N=7915		Labo Nuytinck N=7392		Labo ASZ N=2547	
Premenopausal (18-54 years)	3014	38.1%	2228	30.1%	823	32.3%
Postmenopauzaal (> 54 years)	4901	61.9%	5164	69.9%	1724	67.7%

In the total filtered data set *E. coli* was the most frequently isolated uropathogen (76,6% at AML, 75,9% at Labo Nuytinck and 73,9% at ASZ), followed by *Klebsiella* spp. (7% at AML, 7,9% at Labo Nuytinck and 7,5% at ASZ) (Table 7).

Table 7: Distribution of uropathogens: filtered laboratory data

	AML N= 7915		Labo Nuytinck N=7392		Labo ASZ N= 2547	
E. coli	6061	76.6%	5612	75.9%	1881	73.9%
S. saprophyticus	125	1.6%	229	3.1%	169	6.6%
Klebsiella spp.	553	7.0%	582	7.9%	191	7.5%
Enterococcus spp.	284	3.6%	222	3.0%	60	2.4%
Enterobacter spp.	91	1.1%	56	0.8%	43	1.7%
S. aureus	33	0.4%	30	0,4%	6	0,2%
S. agalactiae	161	2,0%	107	1,4%	7	0,3%
P. mirabilis	225	2,8%	278	3,8%	84	3.3%

Other	382	4.8%	276	3.7%	105	4.1%

Comparative statistical analysis

Comparison between the unprocessed laboratory data and the data from the observational surveillance study

When comparing the raw laboratory data with data from the observational surveillance study, a statistically significant difference ($p < 0,05$) is observed in the distribution of specific uropathogens, particularly *E. coli*, *S. saprophyticus*, *Klebsiella* spp. and *P. mirabilis*. The proportion of *E. coli* isolates is notably higher in the observational study (74,6%) compared to the laboratory datasets (66,6% in AML, 68,2% in Labo Nuytinck and 55,3% in ASZ). A similar trend is observed for *S. saprophyticus*, which also appears more frequently in the observational study data. Conversely, the prevalence of *Klebsiella* spp. and *P. mirabilis* is lower in the observational study compared to the laboratory data, although the numbers in the observational data are very small. No statistically significant differences were observed for the remaining uropathogens (Table 8).

Table 8: Comparison of uropathogens in the observational study and raw laboratory data

	Observational study N= 213 (x, %)		AML N=19472 (x, %, p)			Labo Nuytinck N=14608 (x, %, p)			Labo ASZ N= 20684 (x, %, p)		
E. coli	159	74.6%	12963	66.6%	0.0158	9960	68.2%	0.0414	11432	55.3%	0.0001
S. saprophyticus	17	8.0%	177	0.9%	<0.0001	266	1.8%	<0.0001	356	1.7%	0.0001

Klebsiella spp.	7	3.3%	1850	9.5%	0.0030	1491	10.2%	0.0013	2304	11.1%	0.0004
Enterococcus spp.	14	6.6%	1313	6.7%	0.9215	570	3.9%	0.0700	2156	10.4%	0.0854
Enterobacter spp.	4	1.9%	357	1.8%	0.9616	172	1.2%	0.5363	638	3.1%	0.4147
S. aureus	0	0%	121	0.6%	0.4757	88	0.6%	0.4921	199	1.0%	0.2784
S. agalactiae	1	0.5%	389	2.0%	0.1787	171	1.2%	0.5311	50	0.2%	0.5027
P. mirabilis	2	0.9%	763	3.9%	0.0394	860	5.9%	0.0035	1304	6.3%	0.0021
Other	9	4.2%	1539	7.9%	0.0635	1030	7.1%	0.1420	2245	10.9%	0.0028

Different classification in the observational surveillance study: *Enterococcus faecalis* instead of *Enterococcus* spp., *K. pneumoniae* + *K. oxytoca* instead of *Klebsiella* spp., and *Proteus* spp. instead of *P. mirabilis*

N: number of samples

x: Number of samples sensitive to specific antibiotic

p: p-value

Since *E. coli* is the most prevalent uropathogen in uncomplicated UTIs, this uropathogen was used as a reference for comparing antimicrobial susceptibility. Significant differences (p <0,05) in the susceptibility profiles of *E. coli* between the raw laboratory data and the observational data were found for nitrofurantoin (Labo Nuytinck), amoxicillin-clavulanic acid (AML and ASZ), cefuroxime (all laboratories), quinolones (all laboratories) and cotrimoxazole (ASZ). No statistically significant differences were observed for the remaining antibiotics (Table 9).

A notable observation is the variation in the number of samples tested per antibiotic, which is caused by differences in the antibiograms used by each laboratory. For example, ampicillin

was not included in the antibiograms of AML and ASZ. Since ampicillin is no longer available on the Belgian market, Labo Nuytinck substituted it with amoxicillin. The susceptibility *of E. coli* to both antibiotics is equivalent.

Table 9: Sensitivity of *E. coli* in the observational study and the crude laboratory sample

	Observational study N=159 (x, %)		AML N=12963 (x, n, %, p)				Labo Nuytinck N=9960 (x, n, %, p)				Labo ASZ N=11432 (x, n, %, p)			
Nitrofurantoin	159	100 %	12571	12790	98.3 %	0.1755	9636	9960	96.7 %	0.0371	10585	10852	97.5 %	0.0814
Fosfomycin	158	99.4 %	12879	12879	98.3 %	0.4601	9720	9959	97.6 %	0.2328	11031	11416	96.6 %	0.0908
Amoxi-clavulanic acid	147	92.5 %	8788	12878	68.2 %	<0.0001	8860	9959	89.0 %	0.2048	7514	11421	65.8 %	<0.0001
Quinolones	154*	96.9 %	10688**	12965	82.4 %	<0.0001	8019 ***	9943	80.6 %	<0.0001	9057 ***	11424	79.3 %	<0.0001
Cotrimoxazole	134	84.3 %	10253	12841	79.8 %	0.1984	7794	9959	78.3 %	0.0836	8659	11403	75.9 %	0.0186
Cefuroxime	153	96.2 %	11106	12768	87.0 %	0.0008	4733	9959	47.5 %	<0.0001	10282	11420	90.0 %	0.0137
Ampicillin	87	54.7 %	/	/	/	/	5385	9958	54.1 %	0.9359	/	/	/	/

* was tested for levofloxacin and ofloxacin

** was tested primarily for ciprofloxacin and partially for levofloxacin and ofloxacin

*** was tested for ciprofloxacin

N,n: number of positive samples

x: Number of samples sensitive to specific antibiotic

p: p-value

Comparison between the filtered laboratory data and the data from the observational surveillance study

The distribution of uropathogens in the filtered laboratory data was largely comparable to that of the observational study for *E. coli*, *Enterobacter* spp, *S. aureus*, *S agalactiae* and the group of unnamed uropathogens. The distribution of *S. saprophyticus* was only comparable to that of ASZ, while *P. mirabilis* showed a comparable distribution only with AML and ASZ. A statistically significant difference (p<0,05) was observed in the distribution of *Klebsiella* spp. and *Enterococcus* spp., although the numbers in the observational data are small (Table 10).

Concerning the antimicrobial susceptibility profiles of *E. coli*, no significant differences were observed for nitrofurantoin, with p-values of 0,4045 (AML), 0,0825 (Labo Nuytinck) and 0,4005 (ASZ). Similarly, no statistically significant differences were found for fosfomycin, cotrimoxazole and ampicillin. In contrast, significant differences (p<0,05) were observed for amoxicillin-clavulanic acid (AML and ASZ), quinolones (all laboratories) and cefuroxime (AML and labo Nuytinck) (Table 11).

Table 10: Distribution of uropathogens in the observational study and filtered laboratory data

	Observational study N=213 (x, %)		AML N= 7915 (x, %, p)			Labo Nuytinck N=7392 (x, %, p			Labo ASZ N= 2547 (x, %, p)		
E. coli	159	74.6%	6061	76.6%	0.5664	5612	75.9%	0.7289	1881	73.9%	0.8626
S. saprophyticus	17	8.0%	125	1.6%	0.0001	229	3.1%	0.0002	169	6.6%	0.5416

Klebsiella spp.	7	3.3%	553	7.0%	0.0492	582	7.9%	00193	191	7.5%	0.0315
Enterococcus spp.	14	6.6%	284	3.6%	0.0355	222	3.0%	0.0058	60	2.4%	0.0006
Enterobacter spp.	4	1.9%	91	1.1%	0.3171	56	0.8%	0.1529	43	1.7%	0.7811
S. aureus	0	0%	33	0.4%	1.0000	30	0.4%	1.0000	6	0.2%	1.0000
S. agalactiae	1	0.5%	161	2.0%	0.1332	107	1.4%	0.3745	7	0.3%	0.4745
P. mirabilis	2	0.9%	225	2.8%	0.1343	278	3.8%	0.0252	84	3.3%	0.0621
Other	9	4.2%	382	4.8%	0.8086	276	3.7%	0.8497	105	4.1%	0.9422

Different classification in the observational surveillance study: Enterococcus faecalis instead of Enterococcus spp.*, K. pneumoniae and K. oxytoca instead of Klebsiella* spp.*, and Proteus* spp. *instead of P. mirabilis.*

N: number of positive samples

x: Number of samples sensitive to specific antibiotic

p: p-value

Table 11: *E. coli* sensitivity in the observational study and the filtered laboratory data

	Observational study N=159		AML N=6061 (x, n, %, p)				Labo Nuytinck N=5612 (x, n, %, p)				Labo ASZ N= 1881 (x, n, %, p)			
Nitrofurantoin	159	100%	5957	6011	99.1%	0.4045	5490	5612	97.8%	0.0825	1771	1791	98.9%	0.4005
Fosfomycin	158	99.4%	5967	6039	98.8%	1.0000	5497	5611	98.0%	0.3787	1836	1879	97.7%	0.2526

Amoxi-clavulanic acid	147	92.5%	4295	6042	71.1%	<0.0001	5101	5611	91.9%	05973	1371	1879	73.0%	<0.000
Quinolones	154*	96.9%	5336**	6071	87.9%	0.0009	4812***	5603	85.9%	<0.0001	1657***	1880	88.1%	0.0013
Cotrimoxazole	134	84.3%	4964	6018	82.5%	0.6304	4568	5611	81.4%	0.4157	1505	1864	80.7%	0.3241
Cefuroxime	153	96.2%	5393	5982	90.2%	0.0156	2880	5611	51.3%	<0.0001	1771	1879	94.3%	0.3896
Ampicillin	87	54.7%	/	/	/	/	3293	5611	58.7%	0.3571	/	/	/	/

* was tested for levofloxacin and ofloxacin

** was tested primarily for ciprofloxacin and partially for levofloxacin and ofloxacin

*** was tested for ciprofloxacin

N,n: number of positive samples

x: Number of samples sensitive to specific antibiotic

p: p-value

Comparison between the filtered laboratory data and the unfiltered laboratory data

When comparing the filtered and unfiltered laboratory data, a statistically significant difference ($p<0,05$) in the distribution of uropathogens was observed across all laboratories for *E. coli*, *S saprophyticus*, *Klebsiella* spp., *Enterococcus* spp., *Enterobacter* spp., *P. mirabilis* and the group of unnamed uropathogens. For *S. aureus*, a significant difference was found only in AML and ASZ. No significant differences were found in the distribution of *S. agalactiae* across any of the laboratories (Table 12).

Regarding the antimicrobial susceptibility for *E. coli*, a significant difference ($p< 0,05$) between the filtered and unfiltered data was observed for nitrofurantoin. Apart from fosfomycin in Labo Nuytinck ($p=1540$), all tested antibiotics in all laboratories demonstrated

statistically significant differences in susceptibility between the filtered and unfiltered datasets (Table 13).

Table 12: Distribution of uropathogens in the filtered and raw laboratory data

	AML N filter=7915 N raw=19472					Labo Nuytinck N filter=7392 N raw= 14608					Lab ASZ N filter= 2574 N raw= 20684				
	Filtered (N, %)		Raw (N, %)		p	Filtered (N, %)		Raw (N, %)		p	Filtered (N, %)		Raw (N, %)		p
E. coli	6061	76.6%	12963	66.6%	<0.0001	5612	75.9%	9960	68.2%	<0.0001	1881	73.9%	11432	55.3%	<0.0001
S. saprophyticus	125	1.6%	177	0.9	<0.0001	229	3.1%	266	1.8%	<0.0001	169	6.6%	356	1.7%	<0.0001
Klebsiella spp.	553	7.0%	1850	9.5%	<0.0001	582	7.9%	1491	10.2%	<0.0001	191	7.5%	2304	11.1%	<0.0001
Enterococcus spp.	284	3.6%	1313	6.7%	<0.000	222	3.0%	570	3.9%	0.0008	60	2.4%	2156	10.4%	<0.0001
Enterobacter spp.	91	1.1%	357	1.8%	<0.0001	56	0.8%	172	1.2%	0.0046	43	1.7%	638	3.1%	<0.0001
S. aureus	33	0.4%	121	0.6%	0.0497	30	0.4%	88	0.6%	0.0738	6	0.2%	199	1.0%	0.0003
S. agalactiae	161	2.0%	389	2.0%	0.8831	107	1.4%	171	1.2%	0.0943	7	0.3%	50	0.2%	0.9354
Proteus mirabilis	225	2.8%	763	3.9%	<0.0001	278	3.8%	860	5.9%	<0.0001	84	3.3%	1304	6.3%	<0.0001
Other	382	4.8%	1539	7.9%	<0.0001	276	3.7%	1030	7.1%	<0.0001	105	4.1%	2245	10.9%	<0.0001

Table 13: Sensitivity of *E. coli* between filtered and raw laboratory data

	AML N filter = 6061 N raw = 12963							Labo Nuytinck N filter = 5612 N raw = 9960							Labo ASZ N filter= 1881 N raw= 11432						
	Filtered (x, n, %)			Raw (x, n, %)			p	Filtered (x, n, %)			Raw (x, n, %)			p	Filtered (x, n, %)			Raw (x, n, %)			p
Nitrofurantoin	5957	6011	99.1%	12571	12790	98.3%	<0.0001	5490	5612	97.8%	9636	9960	96.7%	0.0001	1771	1791	98.9%	10585	10852	97.5%	0.0006

Fosfomycin	5967	6039	988%	12659	12879	98.3%	0.0088	5497	5611	98.0%	9720	9959	97.6%	0.1540	1836	1879	97.7%	11031	11416	96.6%	0.0166
Amoxi-clavulanic acid	4295	6042	71.1%	8788	12878	68.2%	<0.0001	5101	5611	90.9%	8860	9959	89.0%	0.0001	1371	1879	73.0%	7514	11421	65.8%	<0.0001
Quinolones	5336*	6071	87.9%	10688	12965	82.4%	<0.0001	4812**	5603	85.9%	8019	9943	80.6%	<0.0001	1657**	1880	88.1%	9057	11424	79.3%	<0.0001
Cotrimoxazole	4964	6018	82.5%	10253	12841	79.8%	<0.0001	4568	5611	81.4%	7704	9959	78.3%	<0.0001	1505	1864	80.7%	8659	11403	75.9%	<0.0001
Cefuroxime	5393	5982	90.2%	11106	12768	87.0%	<0.0001	2880	5611	51.3%	4733	9959	47.5%	<0.0001	1771	1879	94.3%	10282	11420	90.0%	<0.0001
Ampicillin								3293	5611	58.7%	5385	9958	54.1%	<0.0001							

* was tested primarily for ciprofloxacin and partially for levofloxacin and ofloxacin

** was tested for ciprofloxacin

N,n: number of positive samples

x: Number of samples sensitive to specific antibiotic

p: p-value

Discussion

Distribution of uropathogens

E. coli was the most prevalent uropathogen in all first-line settings. This finding is reflected in the results of the observational study as well as in both the filtered and unfiltered datasets. Notably, a statistically significant difference was observed between the unfiltered dataset and the observational data in the distribution of uropathogen species. This discrepancy was present across all laboratories for *E. coli*, *S. saprophyticus*, and *Klebsiella* spp., the three most frequently detected uropathogens.

In contrast, no significant difference was found between the filtered dataset and the observational data for *E. coli*. For the remaining uropathogens, the presence or absence of

significant differences varied per laboratory. These variations can likely be attributed to inconsistencies in uropathogen classification between the observational study and the individual laboratory reporting systems and the small numbers in the observational data.

Antimicrobial susceptibility in *E. coli*

Overall, antimicrobial susceptibility patterns were largely comparable between the filtered dataset and the observational data. None of the laboratories demonstrated statistically significant differences for the most frequently prescribed antibiotics for treatment for uncomplicated UTIs —nitrofurantoin, fosfomycin, and cotrimoxazole—when compared with the observational dataset. A statistically significant difference was, however, observed for quinolone susceptibility in the laboratory data, possibly because of the different quinolones tested depending on the laboratory. For amoxicillin–clavulanic acid, the presence of significant differences between the filtered and observational datasets varied by laboratory.

When comparing the unfiltered dataset with the observational data, no significant differences were identified for nitrofurantoin and fosfomycin, with the exception of nitrofurantoin susceptibility in Labo Nuytinck.

Finally, the comparison of susceptibility results between the unfiltered and filtered datasets revealed statistically significant differences for the most commonly used antibiotics.

Strengths and weaknesses

This study is unique in its design due to the application of a rigorous data-filtering process intended to ensure that the dataset is representative of uncomplicated UTIs in primary care. Previous research has predominantly relied on laboratory datasets that included samples from patients with complicated UTIs or various risk factors, thereby limiting the applicability of

their findings to uncomplicated UTIs. (7,13) For example, antimicrobial susceptibility in the NICE guidelines is primarily based on unfiltered laboratory-derived resistance data. (14)

By contrast, the present study tried to minimize this bias and enhance the validity of its conclusions for first-line clinical practice. To the best of our knowledge, no other studies employing a data-filter have been reported in the literature.

The principal limitation of this study is the inability to directly compare the filtered dataset with independent observational data. As a result, the absence of statistically significant differences should not be interpreted as evidence of equivalence between the datasets. In other words, failure to reject the null hypothesis does not constitute proof that the null hypothesis is true.

If individual-level variables had been available, one possible approach would have been to begin with the unfiltered dataset and subsequently apply predefined inclusion and exclusion criteria. The filtered dataset could then be randomly divided into a training and a testing set (e.g., an 80/20 split) to allow for internal validation. Using this training–testing framework, model-based results could have been compared with the observational findings.

However, due to ethical committee restrictions and the absence of informed consent from patients whose data were obtained from the laboratories, no individual-level variables were available for analysis. As a result, this analytical strategy could not be implemented. Although such an approach would have been particularly relevant given our reliance on laboratory-derived data, the lack of variables limits the scope of the analysis. Consequently, we are unable to perform inferential analyses or draw robust conclusions.

When comparing the raw and filtered datasets, the filtered data appear to be of higher quality. Although no formal conclusions can be drawn from this observation because of the study

design, the findings suggest a trend toward reduced qualitative data and therefore a higher suspected resistance when unfiltered datasets are utilized. The use of unfiltered data may consequently be associated with increased prescription of broad-spectrum antibiotics and a higher prevalence of antimicrobial resistance among uropathogens.

Prospective/relevance

A substitute measure for antimicrobial resistance profiles in primary care may offer a feasible solution. In this study, resistance profiles derived from selected laboratory samples are used. Although the evidence provided by our study is limited, this approach represents an improvement over the current practice, which relies solely on unfiltered laboratory resistance data or labor-intensive observational studies.

The proposed framework envisions that each regional laboratory could annually provide local resistance profiles to general practitioners, based on a predefined and selected sample of isolates. If individual informed consent were required, such an approach would be impractical and unfeasible.

It may also be questioned whether a fully traceable and identical population is strictly necessary when using laboratory data. The primary need is for a sample whose resistance patterns are representative of those observed in uncomplicated urinary tract infections in primary care. A filtering strategy that consistently yields resistance profiles comparable to those in this setting could be sufficient to function as an early warning system for potentially emerging changes in antimicrobial resistance in primary care.

A potential limitation of the filtering approach is that its effectiveness may decrease over time. If general practitioners increasingly adhere to guidelines discouraging urine cultures in

uncomplicated urinary tract infections, the number of eligible samples could theoretically become very small after filtering. (15, 16, 17)

In practice, however, an exact match with the observational study population is not essential. The primary objective is not to construct a perfectly matched cohort, but rather to use this population as an early warning system for emerging resistance. Accordingly, samples from primary care that do not strictly meet the predefined target criteria yet closely approximate, may still be highly informative. Resistance signals may even emerge earlier in this broader subgroup, thereby enhancing the overall sensitivity of the surveillance system.

Conclusion

In practice, guidelines frequently rely on hospital-based data or samples from patients with complicated urinary tract infections, as these cases are more likely to result in laboratory testing than uncomplicated infections. Therefore, laboratory datasets tend to overrepresent complicated cases, which should be considered when interpreting the findings. (7, 13, 14) In this context, a filtering strategy can serve as an effective methodological approach.

References

1. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-20.
2. Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E. The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int. 2010;107(21):361-7.
3. Heytens S, Delvaux N, Christiaens T, De Sutter A. Richtlijn Cystitis bij de vrouw, herziening 2016. Domus Medica.
4. Heytens S, Boelens J, Claeys G, DeSutter A, Christiaens T. Uropathogen distribution and antimicrobial susceptibility in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20-year surveillance. Eur J Clin Microbiol Infect Dis. 2017 Jan;36(1):105–13.
5. Malros K, Huttner B D, McNulty C, Rodrigeuz-Bañoc J, Pulcinic C, Tängdén T et al. Comparison of antibiotic treatment guidelines for urinary tract infections in 15 European countries: Results of an online survey. International Journal of Antimicrobial Agents 2019, 54:478-486.
6. Kornfält Isberg H., Melander E., Hedin K., Mölstad S., Beckman A. Uncomplicated urinary tract infections in Swedish primary care; etiology, resistance and treatment. BMC Infect Dis 2019, 19 (1):155.
7. Chin T L, McNulty C, Beck C, MacGowan A. Antimicrobial resistance surveillance in urinary tract infections in primary care. Journal of Antimicrobial Chemotherapy 2016, 71 (10): 2723–2728.
8. Plate A, Kronenberg A, Risch M, Mueller Y, Di Gangi S, Rosemann T et al. Active surveillance of antibiotic resistance patterns in urinary tract infections in primary care in Switzerland. Infection 2019, 47:1027-1035.
9. Kronenberg A., Koenig S., Droz S., Mühlemann K. Active surveillance of antibiotic resistance prevalence in urinary tract and skin infections in the outpatient setting. Clinical Microbiology and Infection, 2011, 17 (12):1845-1851.
10. Grignon O, Montassier E, Corvec S, Lepelletier D, Hardouin JB, Caillon J, Batard E;EDBAC Study Group. Escherichia coli antibiotic resistance in emergency departments. Do local resistance rates matter? Eur J Clin Microbiol Infect Dis. 2015 Mar;34(3):571-7.
11. Clark AE, Kaleta EJ, Arora A, Wolk DM. Matrix-assisted laser desorption ionization-time of flight mass spectrometry: a fundamental shift in the routine practice of clinical microbiology. Clin Microbiol Rev. 2013;26(3):547–603.
12. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Clinical breakpoints. Available online at: http://www.eucast.org/clinical_breakpoints/
13. Hines MC, Al-Salamah T, Heil EL, Mallemat H, Witting MD, Johnson JK, et al. Resistance Patterns of Escherichia coli in Women with Uncomplicated Urinary Tract Infection Do Not Correlate with Emergency Department Antibiogram. J Emerg Med. 2015;49(6):998–1003.
14. National Institute for Health and Care Excellence. Urinary tract infection (lower): antimicrobial prescribing: National institute for Health and Care excellence (NICE); 2018 [Available from: https://www.nice.org.uk/guidance/ng109.
15. Little P, Moore MV, Turner S, Rumsby K, Warner G, Lowes JA, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. Bmj. 2010;340:c199.
16. Kurotschka PK, Gágyor I, Ebell MH. Acute Uncomplicated UTIs in Adults: Rapid Evidence Review. Am Fam Physician. 2024;109(2):167–74.

17. Markowitz MA, Wood LN, Raz S, Miller LG, Haake DA, Kim JH. Lack of uniformity among United States recommendations for diagnosis and management of acute, uncomplicated cystitis. Int Urogynecol J. 2019;30(7):1187–94.

Persoonlijke reflectie Siebe Vandevelde

Wij (Loic en ik) schreven voor onze masterproef twee publiceerbare artikels over bestaande masterproeven, 'Overview and resistance profile of isolated pathogens in women with uncomplicated urinary tract infection in primary care' en 'Improving Empirical Therapy Guidance: Filtering Laboratory Data to Enhance Surveillance of Uropathogen Resistance'.

We kozen ervoor om beide artikels samen te schrijven en hierin het werk te verdelen i.p.v. elk een artikel voor onze rekening te nemen. Het schrijven van een artikel is best complex. Allereerst is het belangrijk om in te lezen in de literatuur, het bestaande werk goed te begrijpen en na te denken over de structuur en essentie van het artikel. Daarnaast is het belangrijk om wetenschappelijk te leren schrijven en ons te beperken tot de essentie. Ook moesten bronnen worden gezocht en de statistiek worden gecontroleerd. In het laatste artikel was ook een overleg nodig met biostatistiek om de opties en richting van het artikel na te gaan. Uiteindelijk was er ook nog het submissieproces.

Dit alles verliep eigenlijk vrij vlot. We spraken elkaar vaak en werden goed opgevolgd door onze promotor waarmee we ongeveer 2 à 3 maandelijks een meeting hadden. Door steeds korte deadlines voorop te stellen, lukte het goed om de progressie strak te houden en niet uit te stellen. We zaten beiden op dezelfde lijn hierover en wilden graag vooruit. Daarnaast hebben we zelden discussies gehad, zowel bij het verdelen van de taken als bij de richting die we op wilden. Ik denk dat dit kwam door onze communicatie. Ik kende Loic al langer, wat het makkelijker maakt om duidelijk met elkaar te communiceren. Mijn inziens was de verdeling van het werk zeer goed. Ik denk dat dit effectief rond 50/50 zal zijn. De accenten lagen weliswaar wel wat anders, waarbij ik een groter deel van het schrijven van de tekst zelf op mij nam en Loic zich meer met de tabellen, statistiek en submissie bezighield. Toch hebben we deze onderdelen ook grotendeels samen gedaan. Zo waren we ook in de mogelijkheid om in contact te komen met alle aspecten van het maken van een artikel. De vele vergaderingen, het zoeken van artikels, ons inlezen en nadenken over de structuur was werk dat gelijk werd verdeeld. Bij wie het initiatief lag, ging vaak af van wie op welk moment verantwoordelijk was voor een bepaald deel. Indien de ander dan nog niet klaar was of niet rond geraakte, hielpen we elkaar of maakten we een planning. Ik ben dan ook tevreden van de input van ons beide.

Het belangrijkste minpunt van ons beide was denk ik actuëntie. Ik denk dat taken en doelen voorop stellen goed lukte, maar de manier waarop we dit wilden bereiken, deden we vaker op onze eigen manier. Dit lukte, doch denk ik dat met een meer gestroomlijnde methode, we soms makkelijker onze doelen konden bereiken. Bijvoorbeeld bij het zoeken van bronnen was het efficiënter geweest om vooraf na te denken over Mesh terms en bij de statistiek hadden we vooraf kunnen nadenken hoe we hier structuur in konden brengen. Het overleg met biostatistiek was bijvoorbeeld niet goed voorbereid. Niet omdat we hier niet vooraf hadden over nagedacht of het niet voorbereid hadden maar we hadden te weinig gereflecteerd over wat er effectief nodig was om er een vlot overleg van te maken. Daarnaast vind ik dat we elkaar vaker feedback hadden kunnen geven. Eigenlijk kwam deze vooral van de promotor en was dat het sein om zaken anders aan te pakken. We kunnen beide goed om met kritiek, maar zelf vonden we elkaars werk heel vaak goed genoeg (wat niet kan natuurlijk, er zijn altijd werkpunten).

Mijn eigen grootste minpunt was het schrijven van de tekst, ik vond het niet makkelijk om academisch Engels te schrijven, ik denk dat mijn kennis van de Engelse taal hiervoor net tekort

kwam. Naast tips van onze promotor probeerde ik vooral artikels te lezen en op te zoeken welke zinsstructuur wordt verwacht binnen artikels. Vooral het passief schrijven bij iets complexere zinnen kreeg ik moeilijk onder de knie. Uiteindelijk heeft ook AI mij hierin deels geholpen om mijn zinsbouw beter te structureren.

Toch denk ik dat we zeker met tevredenheid mogen kijken naar het resultaat van onze masterproef. Een artikel werd reeds gepubliceerd, het andere is gesubmit bij hetzelfde tijdschrift. Wij hebben weliswaar enkel een steentje bijgedragen in twee grotere projecten waar reeds verschillendeeffici proffen, artsen en HAIO's aan hebben meegewerkt. Toch denk ik dat onze thesis zeker relevant kan zijn binnen de geneeskunde. Antibioticaresistentie is een breed maatschappelijk probleem en het enerzijds bijhouden van resistentieprofielen om erover te waken dat we geen resistentie creëren en anderzijds het zoeken naar manieren om resistentieprofielen van bacteriën te optimaliseren is belangrijk. Dit laatste was vooral een aanzet om hierover na te denken en kan zeker betekenis hebben in de toekomst indien er verder onderzoek naar wordt gedaan.

Ook voor mezelf vond ik het erg relevant om me hierin in te lezen. Uiteindelijk zijn antibioticagidsen in de eerste lijn een erg belangrijk hulpmiddel dat een arts vaak nodig heeft. Als arts is het belangrijk te weten waar deze richtlijnen op gebaseerd zijn. Zelf had ik daar nog te weinig over nagedacht. Ik vond het belangrijk om te weten te komen dat deze data vaak uit labo's afkomstig zijn en het niet evident is om de ongecompliceerde urineweginfecties eruit te filteren. Dit zorgt natuurlijk voor een fout beeld van de resistentieprofielen waarop we ons baseren bij het opmaken van antibioticagidsen. Dit beseffen als huisarts is al een belangrijke stap in de juiste richting, hier een oplossing voor zoeken des te meer.

Persoonlijke reflectie Loic Vanderpoorten

Siebe en ik hebben 2 wetenschappelijke artikels geschreven over reeds bestaande masterproeven van vorige HAIO's. Een artikel ging over het maken van een overzicht van resistentieprofielen bij ongecompliceerde urineweginfecties bij vrouwen in de eerste lijn, het tweede artikel over het filteren van labo-data om de resistentie van uropathogenen te kunnen bewaken. Wat ik het meest meeneem naar de toekomst is onze goede samenwerking en de evolutie van mijn kritische blik op verschillende aspecten zowel binnen de onderwerpen, alsook in de huisartsgeneeskunde in het algemeen.

De samenwerking met Siebe en prof. Dr. Heytens verliep zeer goed. Aangezien Siebe en ik elkaar al kenden voor de start van de masterproef, hadden we er een goed oog op dat de samanwerking vlot ging verlopen en dit werd uiteindelijk bevestigd. We hebben er voor gekozen om samen aan beide masterproeven te werken en niet elk één apart. Dit bleek achteraf ook een goede keuze omdat er meer actieve samenwerking was en er meer mogelijkheden waren om van elkaar te leren. We zaten vaak op dezelfde golflengte en er was weinig tot geen discussie in negatieve zin. Langs beide kanten was er vertrouwen in elkaars aanpak. Een minpunt is misschien dat er soms te weinig kritisch denken naar elkaar toe was, waardoor we er achteraf bekeken nog meer leermomenten hadden kunnen uithalen. Er werd soms minder hard doorgevraagd op elkaars redeneringen, terwijl we dan net onze tekst eventueel nog meer hadden kunnen verdiepen.

De communicatie was zeer open en liep vlot. We konden alles bespreken en zowel inhoudelijke als praktisch waren we goed op elkaar afgestemd. Doordat de inhoudelijke feedback niet altijd even diepgaand was tussen ons onderling, viel een belangrijk deel hiervan uiteindelijk bij onze promotor, die uiteindelijke een belangrijke rol speelde in het starten van constructieve discussies en het meer verfijnen van de artikels. Ook met de promotor verliep de communicatie zeer vlot in tegenstelling tot ervaringen in het verleden. Om de een tot twee maanden was er via Teams een gezamenlijk contact met ons drie, aangevuld met tussentijds mailverkeer dat altijd snel beantwoord werd.

De verdeling van de taken ging eerder organisch en op basis van wat op dat moment nodig was. De eerste stap bestond uit het gezamenlijk doornemen van de literatuur rond het onderwerp, zodat we het bestaande werk goed begrepen en konden nadenken over hoe we dit konden vertalen naar een nieuw, gestructureerd wetenschappelijk artikel. Het wetenschappelijk schrijven zelf was echt een uitdaging voor ons, vooral omdat we moesten leren om data en resultaten helder en gestructureerd weer te geven. Voor het tweede artikel was er ook een overleg met de cel biostatistiek, voor ons een eerste ervaring hiermee. Ten slotte volgde het submissieproces in een wetenschappelijk tijdschrift, wat we elk voor een artikel gedaan hebben. Samengevat was de taakverdeling in grote lijnen gelijk en hebben we ons beiden op alle onderdelen toegespitst. Zelf heb ik de nadruk eerder gelegd op de structuur, tabellen, statistische verwerking en het submissieproces, terwijl Siebe zich meer richtte op het schrijven en de tekstverwerking. In beide aspecten hebben we elkaar goed ondersteund en aangevuld, en het initiatief kwam van beide kanten afhankelijk van het onderdeel waar we op dat moment aan werkten.

Ons gezamenlijk minpunt was efficiëntie. Na elke meeting met de promotor was er steeds een goed idee en een duidelijke richting over hoe het verder moest, maar in de uitvoering verloren

we soms tijd en ging de output van de gesprekken soms wat verloren. Op onze eigen manier kwamen we er uiteindelijk, maar achteraf gezien denk ik dat veel zaken efficiënter hadden gekund. Er hadden duidelijkere afspraken gemaakt kunnen worden, de voorbereiding van het overleg met de cel biostatistiek had grondiger kunnen gebeuren, en we hadden onderling ook kritischer mogen zijn om sneller bij te sturen. Hierdoor hadden we mogelijks tijd kunnen besparen en de kwaliteit van bepaalde stappen nog kunnen verhogen.

Mijn eigen minpunt was het bewaren van overzicht en het systematisch werken aan de thesis. Soms zat er te veel tijd tussen productieve werkmomenten, waardoor ik vaak opnieuw moest hernemen waar we precies stonden en hoe alles in elkaar zat. Dit zorgde ervoor dat er soms onnodig tijd verloren ging en dat de continuïteit in het werk minder was. Achteraf bekeken heeft dit ook een impact gehad op de efficiëntie van de thesis.

Uiteindelijk kijken we met een tevreden blik terug naar ons proces. Er zijn weinig tegenslagen geweest, de samenwerking verliep vlot en uiteindelijk zijn er twee artikels afgewerkt, waarvan één reeds gepubliceerd is en het andere gesubmit werd. Daarnaast geeft het veel voldoening om te beseffen dat we deel uitmaken van een groter geheel, waarbij reeds verschillende HAIO's en professoren de voorbije jaren hebben bijgedragen aan dit onderzoek. We hebben als team een goed resultaat neergezet en een belangrijk leerproces doorgemaakt in onze academische ontwikkeling, onafhankelijk of we hierin verder willen gaan of niet. Tegelijk zie ik waar mijn groeimogelijkheden liggen, zowel op vlak van samenwerking als efficiënt werken. De ervaringen uit dit proces neem ik zeker mee naar de toekomst.