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Computerized Decision Support System (CDSS) Use for Surveillance of Antimicrobial Resistance in Urinary Tract Infections in Primary Care

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TITLE

Computerized decision support system (CDSS) to inform the surveillance of antimicrobial resistance in urinary tract infections in primary care.

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Abstract

Background

Hospital-based surveillance of antimicrobial resistance may be irrelevant to guide antimicrobial use for urinary tract infections (UTIs) in primary care.

Objectives

To highlight the value of online computerized decision support systems (CDSS) in informing surveillance of antimicrobial resistance in community-acquired UTIs.

Methods

We report the susceptibility profile for key antibiotics by type of UTI involving *E. coli* from 2017 to 2020, using queries for UTI (Q-UTI) submitted to a French CDSS. We compare results to the MedQual French surveillance system for community-acquired UTI and the European Antimicrobial Resistance Surveillance Network (EARS-NET) for invasive infections.

Results

We collected 43,591 Q-UTI were collected, of which 10,192 (23%) involved *E. coli*: 40% cystitis, 32% male-UTI, and 27% pyelonephritis. Resistance was 41.3% (95%CI, 40.3%-42.2%) for amoxicillin, 16.6% (95%CI, 15.9%-17.3%) for fluoroquinolones, 6.6% (95%CI, 6.1%-7.0%) for 3CG, and 5.7% (95%CI, 5.2%-6.1%) for aminoglycosides. Resistance to amoxicillin was lower than that reported in MedQual (42.7%, *p*-value=0.004), and in EARS-NET (55.2%, *p*-value<0.001). For fluoroquinolones, resistance was higher than in MedQual (12.0%, *p*-value<0.001) and EARS-NET (15.8%, *p*-value=0.041). In complicated pyelonephritis and male UTI, fluoroquinolones resistance peaked at ~20%. For 3CG, all UTI had higher resistance than in MedQual (3.5%, *p*-value<0.001), but lower than in EARS-NET (9.5%, *p*-value<0.001). Aminoglycosides resistance was not reported by MedQual, and was lower than in EARS-NET (7.1%, *p*-value<0.001).

Conclusion

CDSS can inform in real-time the ecology and surveillance of *E.coli* resistance in community-acquired UTI. In complicated upper UTIs, they underline the risk of empirical use of fluoroquinolones and suggest preferential use of 3CG.

INTRODUCTION

A majority of countries worldwide have national action plans (NAPs) for the prevention of antimicrobial resistance (AMR). [1] Surveillance of AMR is essential at every stage of the NAPs, from initial description to monitoring effects, and subsequently inform clinical guidelines for antimicrobial use (AMU). Routine surveillance of AMR often relies on samples collected in hospitals for individual patient diagnosis with data contributed by hospital laboratories. [2,3] These data may therefore not be representative of the resistance level in the general population, and inappropriate for recommendations at the community level. [3,4] Improving AMR surveillance in primary care would be more relevant, and is now recognized as an objective of interest. [2,5,6]

Urinary tract infections (UTI) are clinical situations where hospital-based surveillance is likely to lead to overestimate AMR, and to the inappropriate choices of antimicrobial therapy for community-acquired infections. [2,6] Indeed, hospital-based surveillance often reports for patients having fail initial empirical therapy, with risks factors for antimicrobial resistance, complications or recurrence. Urinalysis collected among these patients can also bias the reporting of resistance because of the wider range of bacterial species involved in their UTI than in uncomplicated infections. [2] Yet the available AMR surveillance data from the European Antimicrobial Resistance Surveillance System network (EARS-NET) only reports hospital-based data aggregated over blood, and cerebrospinal fluid samples irrespective of the underlying pathology (urinary tract infections, pneumonia, wound infections, ...). [7] More relevant data is available from the French (MedQual) surveillance network for community-acquired UTI in biological laboratories, but cannot be stratified by infection type or patient's characteristics. [8–10]

Joint information on resistance level by type of UTI may however be readily obtained using the case description submitted by practitioners to an online computerized decision support system (CDSS) for antimicrobial prescribing. [11] In those, detailed information on the type of UTI and microbiology is input at the point of care to assist clinical decision-making and improve antimicrobial prescription. It has the potential to reduce the likelihood of recall bias related to surveillance based on the retrospective collection of cases.

We hypothesized that data submitted to *Antibioclic* – a French online guideline-based CDSS for antimicrobial prescribing extensively used in primary care (http://www.antibioclic.com) – would allow describing resistance level by infection type in community-acquired UTI due to *E. coli*. [12]

Here, we report the susceptibility profile for key antibiotics by type of UTI involving *E. coli* from 2017 to 2020. We then compare it to that obtained by the MedQual French surveillance system for community-acquired UTI, and by EARS-NET for invasive infections.

MATERIAL AND METHODS

Objectives

We aimed to highlight the added value of online computerized decision support systems (CDSS) for antimicrobial prescribing in primary care to inform the surveillance of antimicrobial resistance in community-acquired UTIs involving *E. coli*.

Study design

We conducted a cross-sectional analysis of *Antibioclic* data, prospectively collected from November 2017 (week 47) to September 2020 (week 37). [12]

Description of the CDSS extension for UTI

Antibioclic was developed by academics and released in October 2011. Its access and use are free of charge. It relies on a Task-Network Model (TNM) to translate national guidelines into an easy-to-use system described elsewhere. [12] An academic steering committee monitors official updates of national guidelines for each pathology/infectious disease.

In late 2017, we extended *Antibioclic* with a module for patient-specific recommendations of antimicrobial therapy for UTI. Access to this module was possible upon registration. The UTI targeted by the system included asymptomatic bacteriuria in pregnant women, cystitis (in children, uncomplicated and complicated in adults), pyelonephritis (in children, uncomplicated and complicated in adults), and male UTI. Users could input characteristics of patients, results of urine culture (when available), and exposure to fluoroquinolone within the last 6 months to individualize the proposition for antimicrobial therapy. In all cases, users were free to follow or not the CDSS proposition for antimicrobial therapy. Previous cross-sectional surveys showed that 96% of users reported CDSS assistance during the last consultation. *Antibioclic* was systematically used for initiation of an antibiotic course by 24% of users, and 93% reported having followed the CDSS recommendation for the latest prescription. Most GPs were comfortable using the CDSS in front of a patient. [12]

Data

We defined a query for urinary tract infection (Q-UTI) as a query performed to the CDSS for the antimicrobial therapy of a UTI. The data describing a Q-UTI included user's characteristics, patient's characteristics (age group, type of UTI type, history of UTI, recent exposure to antibiotics, hospitalization and travel abroad within the last year), and pathogen / antimicrobial resistance profile. Q-UTI data were recorded at the point-of-care during CDSS consultation. Q-UTI were classified according to guidelines of the European Association of Urology and the French Infectious Disease Society (SPILF) [13,14]. When urinalysis was not performed or registered for managing infection, the Q-UTI was considered as not documented. Antimicrobial resistance profile of Q-UTI was established by primary care laboratories working with physician using the CDSS. Susceptibility testing result was reported by physician using the CDSS, according to guidelines from the French microbiology society ("Comité de l'Antibiogramme de la Société Française de Microbiologie", CA-SFM) aligned on the European Committee on Antimicrobial Susceptibility Testing (EUCAST). [15]

We collected the 2017 to 2019 data on *E. coli* resistance to key antibiotics (amoxicillin, third-generation cephalosporin – 3CG, fluoroquinolones – FQ, and aminoglycosides) from the EARS-NET for invasive infections and the French MedQual network for primary care urine cultures (last data available for both networks) [7–10]. EARS-NET reports aggregated resistance issued from blood and cerebrospinal fluid, regardless of the underlying pathology (urinary tract infections, pneumonia, wound infections…). [7] EARS-NET for France relied on three networks cumulating a maximum of 59 health institutions laboratories over surveyed period: 23 from teaching hospitals, 30 general hospitals, 3 military hospitals, and 3 private hospitals. Duplicates are eliminated, data aggregated and sent to EARS-NET for external quality assessment in collaboration with the United Kingdom National External Quality Assessment Service (NEQAS-EARS). [16] The representativeness for national population coverage of hospitals and population was ranging from 20% to 22% over study period.[7,8] The MedQual network reports aggregated resistance issued from random urine culture performed in primary care, regardless of the underlying pathology and does not report on aminoglycosides. MedQual relied on 610 to 1016 private practice laboratories in all 13 regions of France during survey period, with 18% to 25% representativeness of private practice laboratories, and population. Regional resistance levels for fluoroquinolones, and 3CG in *E. coli* are only available for year 2019. Results of susceptibility tests are monthly collected in the MedQual database centre for validation and analysis. [8–10]

Statistical analysis

We restricted the analysis to Q-UTI performed by primary care users, involving *E. coli* and regarding cystitis, pyelonephritis in adults except for pregnant women, and male UTI. We first described the characteristics of patients by type of UTI. Then we computed the 95% confidence interval (95%CI) for the percentage of resistance to amoxicillin, 3CG, FQ, and aminoglycosides in *E. coli*, in data issued from our CDSS-extension. We compared the resistance level to the one issued from MedQual and EARS-NET, using crude prevalence ratio and the chi-squared test. All tests were two-tailed and the level of significance was set at 5%. Analysis was performed on R, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics, policies, and funding

Antibioclic is edited and administered by a not-for-profit organization which is not linked to any pharmaceuticals companies, neither for the contents of the CDSS nor for funding. The steering committee members are volunteers and conflicts of interest of members are disclosed on the website. The funding used to develop the CDSS-extension was obtained from a competitive call of Paris area health authorities. None of the collected data are shared with private companies. The confidentiality policy is fulfilling with European General Data Protection Regulation. The study has been approved by the ethics committee of the CNGE (N° 16051997).

RESULTS

CDSS registered users

During the three years of study, 3,494 medical doctors registered to the CDSS-extension, of which 2,996 (86%) were general practitioners (GPs), and 2,622 (75%) were from the Ile-de-France area. Users were 52 years old in median [IQR, 40 to 61], and 1,861 (53%) were women. Most were working in group practices or health centers (2,256 – 65%). Compared to national data, GPs characteristics were similar for age, with a higher rate of females (53% versus 48%) and GPs-trainer (29% versus 8%). [17,18] Two-third users (2,385 – 68%) reported using the previous version of the CDSS (before 2017) and consulting the CDSS in 40% [IQR, 15 to 70] of cases in which they initiated an antibiotic therapy.

UTI due to *E.coli* in CDSS-extension

The registered users submitted 43,591 Q-UTI to the system during the study period, with a median of 8 Q-UTI [IQR, 2 to 32] per user. A total of 38,862 Q-UTI (91%) concerned adult patients, 16,249 (42%) were documented by a urine culture, and 10,192 (64%) involved *E. coli*, and were therefore included in the statistical analysis: cystitis in 4,174 (41%), male UTI in 3,226 (32%), and pyelonephritis in 2,792 (27%). Table 1 shows the characteristics of patients by type of UTI involving *E. coli*. More than a third of Q-UTI (4,066 – 40%) occurred in the elderly (age ≥ 65 years), 2,081 (20%) in patients who had received antibiotic therapy in the 3 months before, and 831 (8%) in patients who presented repeated UTI. In complicated cystitis, complicated pyelonephritis or male UTI, patients were older, likely to live in nursing homes, had higher rate of repeated UTI, had been recently hospitalized, or recently received antibiotics (Chi-squared tests, p-values <0.001).

Resistance to key antibiotics

Among the 10,192 *E. coli* strains described in the Q-UTI, resistance to amoxicillin was present in 4,208 (41.3%; 95%CI, 40.3 to 42.2%), to fluoroquinolones in 1,691 (16.6%; 95%CI, 15.9 to 17.3%), to 3CG in 681 (6.6%; 95%CI, 6.1 to 7.0%), and to aminoglycoside in 578 (5.7%; 95%CI, 5.2 to 6.1%). Overall, cross-resistance to 3CG and fluoroquinolones was present in less than 10% of Q-UTI. The resistance increased in complicated upper UTIs, reaching ~20% for fluoroquinolones in complicated pyelonephritis and male UTI (Figure 1).

Comparison with surveillance networks for antimicrobial resistance

The resistance levels to the antibiotics were stable over the years within our CDSS and established surveillance systems (Cochran-Armitage tests, p-values >0.050). Figure 1 shows the resistance level of studied antibiotics by type of UTI within our CDSS, and in other surveillance systems.

Amoxicillin

The overall resistance to amoxicillin in *E. coli* identified in our system *(*41.3%) was lower than that reported in MedQual (42.7%, prevalence ratio = 0.93 (95%CI, 0.96 to 0.98), *p*-value =0.004), and in EARS-NET (55.2%, prevalence ratio = 0.75 (95%CI, 0.74 to 0.76), *p*-value <0.001).

Fluoroquinolones

For fluoroquinolones, overall resistance (16.6%) was higher than in MedQual (12.0%, prevalence ratio = 1.38 (95%CI 1.38 to 1.39), *p*-value <0.001) and EARS-NET (15.8%, prevalence ratio = 1.05 (95%CI 1.05 to 1.06), *p*-value = 0.041). This higher resistance for fluoroquinolones was found in all types of UTIs but uncomplicated cystitis, and ranged from 14.3% to 20.4%. The prevalence ratios ranged between 0.91 and 1.70.

Third generation cephalosporins

For 3CG, all types of UTI had higher resistance rate than in MedQual (6.6% versus 3.5%, prevalence ratio = 1.90 (95%CI, 1.90 to 1.91), *p*-value <0.001). It ranged from 4.8% to 10% and corresponded to prevalence ratios of 1.37 to 2.86. Conversely, resistance to 3CG was lower than that reported by EARS-NET (6.5% versus 9.5%, prevalence ratio = 0.68 (95%CI, 0.68 to 0.69), *p*-value <0.001).

Amynoglycosides

Overall, resistance to aminoglycosides was lower in our system than in EARS-NET (5.7% versus 7.1%, prevalence ratio = 0.80 (95%CI, 0.79 to 0.80), *p*-value <0.001). Most significant variation were for uncomplicated cystitis (4.4%, *p*-value <0.001) and pyelonephritis (4.5%, *p*-value <0.001), while it was similar to EARS-NET for other UTIs (Figure 1). MedQual was not reporting resistance to aminoglycosides.

DISCUSSION

Community-acquired UTI involving *E. coli* submitted to our CDSS showed a gradient of resistance from uncomplicated cystitis to complicated pyelonephritis and male UTI. Antimicrobial resistance was higher than that derived from random urine cultures but close to EARS-NET for invasive infections. We found a concerning rate of resistance to fluoroquinolones in complicated pyelonephritis and male UTI, around 20%.

Gradient of resistance

The existence of a gradient of resistance in *E. coli*, suggests that the location (lower versus upper) and the type (uncomplicated versus complicated) of UTI could be used as a proxy for levels of resistance. Resistance is likely to occur in upper complicated UTIs. [19–22] These parameters could inform the choice of empirical therapies in primary care and accelerate prescription of more potent antimicrobial therapy. This is of interest, considering that in elderly patients experiencing UTI in primary care, a deferred antimicrobial therapy increases bloodstream infection rate and all-cause mortality. [23]

Resistance to fluoroquinolones and 3CG

Consistent with surveillance data and the literature, resistance to fluoroquinolones and 3CG increased from uncomplicated cystitis to complicated upper UTIs [3,7–10,20,24–27]. The high frequency of resistance to fluoroquinolones in complicated upper UTIs (~20%) raises concerns regarding the empirical use of oral fluoroquinolones for managing these infections in primary care [19,28]. It highlights that resistance level in clinically relevant infection in primary-care may be close to that observed in hospital settings. Primary care driven data issued from CDSS could inform stakeholders for monitoring the effect of NAPs on AMR, and developing guidelines on AMU in community-acquired UTI. [1–3,6] Indeed, injectable 3CG and oral fluoroquinolones are often both recommended as first-line antibiotics in uncomplicated and complicated upper UTIs. [6,13,14] The preferential use of injectable 3CG over oral fluoroquinolones is recommended whenever the resistance to fluoroquinolones reaches 10% or higher. [6,13,14] Such guidelines are developed in a hospital-based perspective where physicians are aware of the local resistance rate, and have access to susceptibility testing. They may be not suitable for primary care, where GPs can be unaware of national and local resistance rates, and lack access to point-of-care susceptibility testing. [29] One may then suggest that dual recommendations can mislead GPs towards the prescription of an oral antibiotic over an infused antibiotic. Reducing the FQ/3CG ratio in primary care is thereby unlikely, as illustrated by the high use of oral fluoroquinolones for UTI in primary care. [30,31]

Limits to comparisons between surveillance systems

The rate of empirical antimicrobial prescriptions was lower (60% versus 97%) than in a recent French survey enrolling women with a similar rate of documented UTI. [32] GPs may indeed consult the CDSS less frequently in infections without urine culture, as the guidelines are simpler than when a documentation is available. This preferential use of the platform for challenging situations could overestimate resistance in our system. The sampling properties of the surveillance systems used are ill characterized, and the differences in sampling methods across surveillance systems can bias resistance estimates and comparisons. [1–3,6,24] It is acknowledged that in EARS-NET, underreporting of susceptible isolates can occur for blood cultures, resulting in an overestimation of resistance. [16] Also, UTIs are not specifically targeted in EARS-NET, while in France the urinary tract is the most frequent portal of entry for bloodstream infection. EARS-NET may represent a worst-case scenario for resistance in the community. Its use may reduce the likelihood of misinforming guidelines on AMU in primary care, but data like we provide are more relevant. [33] Looking at Q-UTI submitted to our CDSS allows describing the nature and frequencies of UTIs seen in general practice, where the prescription is required. In our system, Q-UTI are submitted by participating GPs prospectively, which limits recall bias. It jointly described the pathology and the germs, providing more details than in two other systems. Despite differences in sampling, the resistance levels were in the range observed between random urine cultures, and invasive infections. [7–10] The comparison of resistance levels between networks is also hampered by the differences in periods for data collection, with older data for MedQual and EARS-NET when our estimates are nearly real-time. The resistance levels to the antibiotics were stable over the years within our system and established surveillance systems. Combined with the slow change in antimicrobial resistance in France, this support that recent changes are unlikely to explain the differences between these data sources. [7–10] Finally, most users of the CDSS were concentrated in the "Ile-de-France" area, where antibiotic consumption is larger than in France as a whole: 23.8 defined-daily doses per 1000-inhabitants in Ile-de-France versus 22.5 for the rest of the country in 2018 for primary care. [34] However, 2019 resistance data from the national program for surveillance of antimicrobial resistance in primary care shows that resistance levels in our system falls in the range observed among *E. coli* at regional level; from 6.8% to 15.3% for fluoroquinolones (11.0% in “Ile-de-France”), and from 2.4% to 5.8% for 3CG (5.3% in “Ile-de-France”).[10] Resistance levels observed within our CDSS are thereby likely to be paralleled to the French situation.

Conclusion

We presented data on *E. coli* resistance to antibiotics collected in primary care using a CDSS for antimicrobial prescription. This can inform in real-time on the ecology and surveillance of *E.coli* resistance in community-acquired UTI. Such data could be embedded in existing surveillance systems. They underline the risk of empirical use of fluoroquinolones in complicated upper UTIs and suggest a preferential use of 3CG in such settings. The future linkage between diagnosis, resistance, and prescription is needed to better describe and inform antimicrobial use through individualized guidelines for the prescription.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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Access to data: Academic researchers can access the data for 12 months after the publication of results. Transfer to countries outside of the EU is not allowed. A formal request had to be sent to the corresponding author.

Author's contribution: TD: Conceptualization, Funding acquisition, Project administration, Data Curation, Formal analysis, Visualization, Original Draft Preparation. JLB: Interpretation of data, Review and editing. SL: Interpretation of data, Review and editing. NPS: Interpretation of data, Review and editing. FXL: Interpretation of data, Review and editing. EB: Interpretation of data, Review and editing. PJ: Interpretation of data, Review and editing. FT: Interpretation of data, Original Draft Preparation, Supervision, Review and editing. PYB: Conceptualization, Interpretation of data, Original Draft Preparation, Supervision, Review and editing

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TABLES AND FIGURES

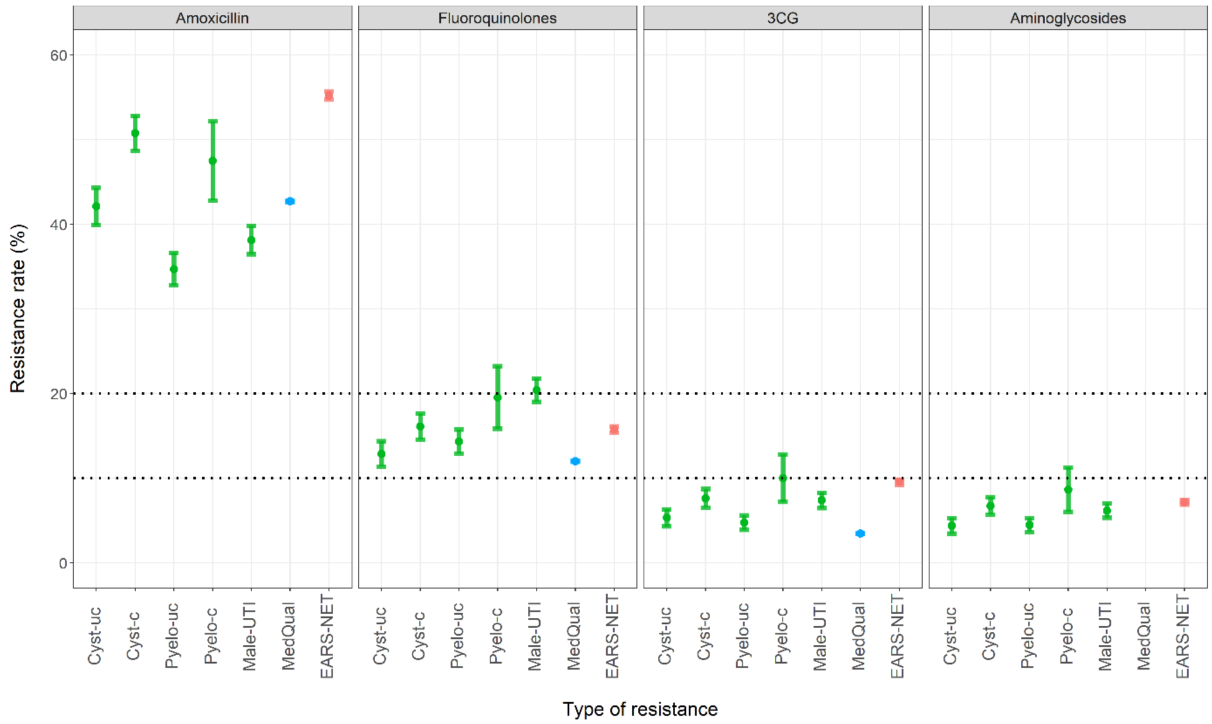
Table 1: Patient's characteristics by type of UTI.

Patients' characteristics	Cystitis		Pyelonephritis		Male UTI	*p*-value [‡]
	Uncomplicated	Complicated [†]	Uncomplicated	Complicated [†]		
	N = 1,919	N = 2,255	N = 2,352	N = 440	N = 3,226	
Age ≥ 65 years	539 (28.1%)	1,796 (79.6%)	304 (12.9%)	275 (62.5%)	1,152 (35.7%)	<0.001
Living in nursing home	23 (1.2%)	140 (6.2%)	12 (0.5%)	35 (8.0%)	46 (1.4%)	<0.001
Repeated UTI	176 (9.2%)	346 (15.3%)	113 (4.8%)	42 (9.5%)	154 (4.8%)	<0.001
Antibiotic intake within 3 months	445 (23.2%)	730 (32.4%)	302 (12.8%)	95 (21.6%)	509 (15.8%)	<0.001
Fluoroquinolones within 6 months	347 (18.1%)	568 (25.2%)	424 (18.0%)	139 (31.6%)	845 (26.2%)	<0.001
Traveled abroad within 12 months	30 (1.6%)	31 (1.4%)	54 (2.3%)	10 (2.3%)	82 (2.5%)	0.016
Hospitalization within 12 months	87 (2.3%)	372 (9.1%)	53 (1.9%)	57 (10.1%)	366 (7.2%)	<0.001

[†] Excluding infections in pregnant women.

[‡] Chi-squared comparison of patients' characteristics among uncomplicated cystitis (reference class) to other types of UTI: complicated cystitis, uncomplicated pyelonephritis, complicated pyelonephritis, and male UTI.

Figure 1: Resistance rate to amoxicillin, third-generation cephalosporin, fluoroquinolones, and aminoglycosides, in E. coli, by type of UTI in CDSS-extension and compared to MedQual and EARS-NET data.



The estimation of resistance of *E. coli* to amoxicillin, fluoroquinolones, 3rd generation cephalosporin (3CG), and aminoglycosides are reported from three sources of data: CDSS-extension for documented urinary tract infection (green), MedQual for urine analysis in outsettings (blue), and EARS-NET for invasive infections (red). Estimates are shown with a 95% confidence interval. The dotted lines correspond to resistance rates of 10% and 20%, respectively. The following abbreviations are used: “Cys-uc” for uncomplicated cystitis; “Cys-c” for complicated cystitis; “Pyelo-uc” for uncomplicated pyelonephritis; “Pyelo-c” for complicated pyelonephritis; and “Male-UTI” for male urinary tract infection.