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Regional variations in antimicrobial susceptibility of community-acquired uropathogenic *Escherichia coli* in India: Findings of a multicentric study highlighting the importance of local antibiograms

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ABSTRACT

Objectives: Evidence-based prescribing is essential to optimize patient outcomes in cystitis. This requires knowledge of local antibiotic resistance rates. Diagnostic and Antimicrobial Stewardship (DASH) to Protect Antibiotics (https://dashuti.com/) is a multicentric mentorship program guiding centers in preparing, analyzing and disseminating local antibiograms to promote antimicrobial stewardship in community urinary tract infection. Here, we mapped the susceptibility profile of *Escherichia coli* from 22 Indian centers.

Methods: These centers spanned 10 Indian states and three union territories. Antibiograms for urinary *E. coli* from the outpatient departments were collated. Standardization was achieved by regional online training; anomalies were resolved via consultation with study experts. Data were collated and analyzed.

Results: Nationally, fosfomycin, with 94% susceptibility (inter-center range 83-97%), and nitrofurantoin, with 85% susceptibility (61-97%), retained the widest activity. The susceptibility rates were lower for co-trimoxazole (49%), fluoroquinolones (31%), and oral cephalosporins (26%). The rates for third- and fourth-generation cephalosporins were 46% and 52%, respectively, with 54% (33-58%) extended-spectrum β-lactamase prevalence. Piperacillin-tazobactam (81%), amikacin (88%), and meropenem (88%) retained better activity; however, one center in Delhi recorded only 42% meropenem susceptibility. Susceptibility rates were mostly higher in South, West, and Northeast India; centers in the heavily populated Gangetic plains, across north and northwest India, had greater resistance. These findings highlight the importance of local antibiograms in guiding appropriate antimicrobial choices.

Conclusions: Fosfomycin and nitrofurantoin are the preferred oral empirical choices for uncomplicated *E. coli* cystitis in India, although elevated resistance in some areas is concerning. Empiric use of fluoroquinolones and third-generation cephalosporins is discouraged, whereas piperacillin/tazobactam and aminoglycosides remain carbapenem-sparing parenteral agents.

Introduction

Urinary tract infections (UTIs) are among the most frequent infections worldwide. About 60% of women and 20% of men will experience at least one UTI during their lifetime, prompting antibiotic treatment, usually prescribed empirically [1,2]. *Escherichia coli* remains the predominant pathogen worldwide in community- and hospital-acquired settings [3]. Increasing resistance complicates treatment, making outcomes uncertain, even in simple cystitis [4].

Minimizing resistance needs multi-disciplinary stewardship approaches [4]. These include evidence-based prescribing, which requires knowledge of local community and hospital antibiotic resistance rates. In India, much prescribing is market-driven rather than evidence-based. This situation prompted us to develop Diagnostic and Antimicrobial Stewardship (DASH) to Protect Antibiotics (https://dashuti.com/).

DASH is a multicentric mentorship-based study that aims to assemble and disseminate antibiogram data and to promote greater interaction between microbiologists and clinical practitioners to improve antimicrobial prescribing. The present investigation involved 22 centers across India and sought to collect, review, and optimize antibiogram data for community-acquired UTI due to *E. coli*. DASH's further approaches include vignette-based questionnaires and focused education.

Methods

Center recruitment

This ongoing study was open to all interested centers across India, including public and private medical colleges, tertiary health care facilities, and standalone laboratories. Invitations to participate were sent by email and WhatsApp and through LinkedIn. A total of 41 centers were approached, of which 29 (27 tertiary care public and private hospitals and two private laboratories) agreed to join. Five hospitals and private laboratories subsequently withdrew, citing lack of time or internal support, leaving 22 sites: 11 were in north (N) India, one in Jammu & Kashmir (extreme north), four in Delhi, one in the neighboring National Capital Region (NCR) Gurugram, one each in Aligarh and Chandigarh and three in Lucknow, five in south (S) India (two in Chennai and one each in Pondicherry, Karnataka, and Kerala), and three in west (W) India (two in Gujarat and one in Mumbai), along with single centers in the east (E) (Patna), northeast (NE) (Guwahati), and central India (Bhopal) (Figure 1). Due to proximity, Chandigarh (a union territory west of Delhi) and Gurugram (in Haryana but part of the NCR) were analyzed together with the Delhi sites (Supplementary Table S1). The "Delhi" region sites (except Chandigarh) are located in the Gangetic plains, along with Aligarh, Lucknow (with three sites), and Patna. A total of 17 centers were academic, whereas five were non-academic. Ten states and three union territories participated. The duration of this study was 1 year, from January 1, 2022 to December 31, 2022.

Ethical approval for the study was obtained by the centers. Details of the centers' infrastructure and routine practices were collated via a questionnaire.

Initial actions to achieve standardization of methods

Before preparing the outpatient department-based antibiograms, a workshop on implementation of the WHONET and BACLINK susceptibility data analysis software (https://whonet.org) was conducted by three centers [2]. This was filmed and made available to all sites (links are: https://youtu.be/h_zWyWobtPw , https://youtu.be/ijSFlIy5DZ4 , https://youtu.be/wh7XlsxKmJg). The centers remained free to prepare their antibiograms using other tools, if preferred.

Sample processing at study sites

Microscopy for bacteria and leucocytes was the most common initial screen, used at 14 sites; five sites used the dipstick method and three

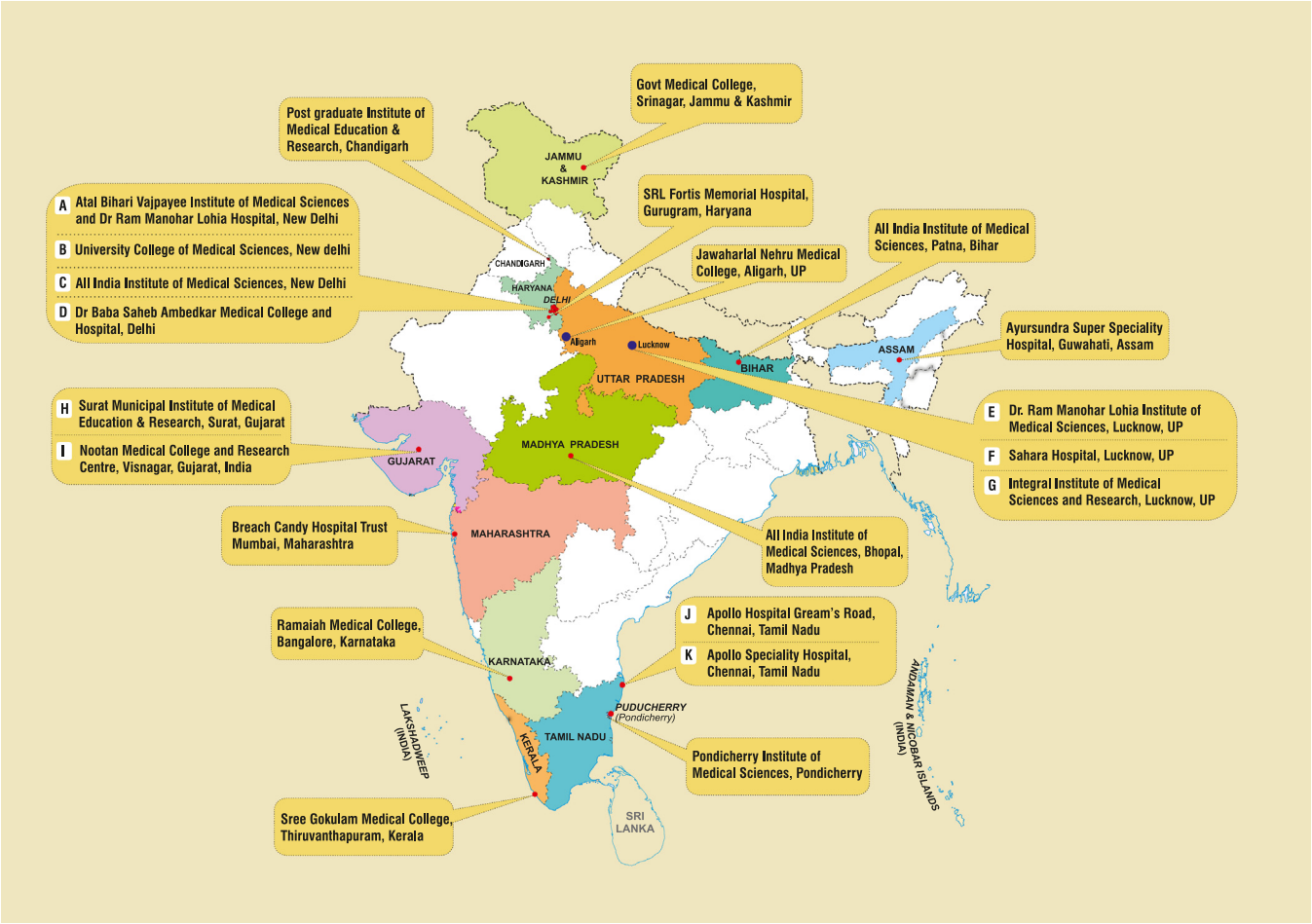

Figure 1. Participating states and centers.

screened by visual examination of urine turbidity. A total of 12 centers used automated bacterial identification for putatively infected urines; 10 used classical manual methods [5]. Antimicrobial susceptibility testing was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines (M100-Ed33) 2022 [6]. A total of 10 sites largely used disc diffusion testing, whereas 12 used automated systems and six used a mixture of both approaches. Quality control was practiced by all laboratories. Extended-spectrum β-lactamases (ESBLs) were detected using cephalosporin/clavulanic acid synergy tests by eight centers.

CLSI urine break points were used for interpretation of cefazolin and cefuroxime results. Isolates with susceptibility reaching the dose-dependent breakpoints, such as to cefepime, were counted as susceptible.

Data collection, handling, review, and validation

Only clinical isolates from patients presenting with a symptomatic UTI at an outpatient or emergency department were included.

Data from such patients were collated into site antibiograms if 30 or more non-duplicate isolates were tested at the site. Only data for routinely tested antimicrobial agents were included. CLSI guideline M39A4E CLSI 2022 was used to prepare the antibiograms [3,7]. Once the data were collected, exhaustive region-wide online sessions were conducted, involving Prof Livermore, to analyze them and to resolve anomalies (e.g. lower percent susceptibilities) for (i) amikacin compared with gentamicin; (ii) ceftriaxone, cefotaxime, and ceftazidime compared with cefuroxime; (iii) cefuroxime compared with cefazolin; (iv) piperacillin/tazobactam compared with amoxicillin/clavulanic acid; (v) meropenem compared with ertapenem and/or piperacillin/tazobactam; and (vi) ciprofloxacin compared with levofloxacin.

Statistics

Antimicrobial susceptibilities of the *E. coli* isolates were compared across six broad geographic regions comprising N, S, E, NE, W, and central India. The overall susceptibility was calculated, and the proportions of susceptible isolates were compared between regions (z test for proportions). Representative drugs from different antimicrobial drugs (fosfomycin, nitrofurantoin, trimethoprim-sulfamethoxazole, cefotaxime, ceftriaxone, gentamicin, meropenem, ciprofloxacin, piperacillin/tazobactam, and cefepime) were subjected to detailed statistical analysis. To obtain a measure of the degree of inter-regional variability, the intra-cluster correlation (ICC) was calculated based on a random intercept logistic regression model using SPSS version 23 IBM and R version 4.0 and Excel. Medians were calculated. The arithmetic and harmonic means were calculated to average percentage susceptibility rates reported by different sites. Because percent susceptibilities are ratios, harmonic means were preferred; however, the results were similar, regardless of which type of average was used (Table 1). "Resistance to third-generation cephalosporins" is the harmonic mean of individual sites' resistance rates to ceftazidime, cefotaxime, ceftriaxone, and cefixime; that for "β-lactam/b-lactamase inhibitors" is for piperacillin/tazobactam and cefoperazone/sulbactam

Table 1
Antibiotics tested and nationwide antimicrobial susceptibility profile of *Escherichia coli* isolated from outpatients.

					Resistance rates across different centers			
Total no. centers = 22	**No. of centers testing the drug**	**% of centers testing the drug**	**Total no. of isolates tested**	**% of all isolates tested with drug**	**Nationwide average % susceptibility**	**Arithmetic mean %**	**Harmonic mean %**	**Median**
Nitrofurantoin	22	100	7790	100%	86%	86%	85%	86%
Fosfomycin	10	45	4165	53%	95%	95%	94%	95%
Trimethoprim-Sulfamethoxazole	19	86	6639	85%	49%	49%	48%	48%
Ampicillin	11	50	3871	50%	21%	21%	20%	21%
Cefazolin	4	18	3369	43%	26%	26%	26%	26%
Cefuroxime	9	41	3166	41%	26%	26%	25%	26%
Cefoxitin	2	9	538	7%	41%	41%	41%	41%
Cefepime	11	50	4999	64%	53%	53%	52%	51%
Ceftazidime	11	50	3871	50%	55%	55%	54%	54%
Cefotaxime	9	41	3369	43%	47%	47%	47%	47%
Ceftriaxone	11	50	2645	34%	48%	48%	46%	48%
Cefixime	3	14	530	7%	41%	41%	41%	41%
Cefoperazone	1	5	222	3%	18%	18%	18%	18%
Ampicillin-Sulbactam	4	18	683	9%	31%	31%	29%	31%
Amoxicillin-Clavulanic acid	11	50	4307	55%	47%	47%	47%	48%
Piperacillin-Tazobactam	17	77	5242	67%	81%	81%	81%	81%
Cefoperazone/sulbactam	7	32	4094	53%	79%	79%	79%	79%
Imipenem	16	73	6203	80%	88%	88%	88%	89%
Meropenem	19	86	7064	91%	89%	89%	88%	91%
Gentamicin	19	86	6834	88%	76%	76%	76%	77%
Amikacin	20	91	6945	89%	88%	88%	87%	89%
Norfloxacin	9	41	3425	44%	29%	29%	28%	29%
Levofloxacin	8	36	3313	43%	41%	41%	35%	41%
Ciprofloxacin	19	86	6712	86%	33%	33%	29%	34%

Key:	
Fewer than 33% of isolates tested	
Adequate proportion of isolates tested: % susceptibility	
>90%	
81-90%	
71-80%	
61-70%	
40-60%	
<40%	

Table 2
Proportion of susceptible *E. coli*, with 95% confidence interval, and pairwise comparisons across six regions of India.

Drug	North A	South B	West C	East D	North-East E	Delhi-NCR F	Overall Susceptibility	Intra-cluster correlation
Fosfomycin **(N = 3187)**	92.0% (90.5; 93.5)	97.0% (92.3; 97.7) [a]**A**	95.4% (91.0; 99.7)	—	93.1% (83.9; 102.3)	95.0% (93.7; 96.3)	93.6% (88.6; 96.6)	0.92
Nitrofurantoin **(N = 6570)**	81.0% (79.3; 82.7) [a]**D**	88.0% (86.8; 89.2) [a]**A** [a]**D**	93.1% (91.4; 94.8) [a]**A**[a]**B**[a]**D**[a]**F**	69.0% (64.9; 73.0)	96.6% (90.0; 103.2) [a]**D**	86.7% (85.4; 88.0) [a]**A**[a]**D**	86.6% (79.8; 92.0)	0.85
Trimethoprim-Sulfamethoxazole **(N = 5472)**	43.0% (39.2; 46.8)	59.0% (57.2; 60.8) [a]**A**[a]**C**[a]**D**[a]**F**	52.0% (46.7; 55.3) [a]**A**[a]**D**[a]**F**	36.8% (32.6; 40.9)	58.6% (40.7; 76.5)	41.0% (39.0; 42.9)	45.6% (38.4; 53.6)	0.46
Cefotaxime **(N = 3336)**	52.8% (45.7; 59.9) [a]**B**[a]**D**[a]**F**	39.9% (38.0; 41.7) [a]**D**[a]**F**	85.1% (77.7; 92.4) [a]**A**[a]**B**[a]**D**[a]**F**	27.0% (23.3; 30.7)	—	29.0% (26.8; 31.2)	47.1% (24.0; 72.2)	0.36
Ceftriaxone **(N = 2645)**	38.0% (35.7; 40.3)	46.9% (43.5; 50.3) [a]**A**	61.1% (58.2; 64.1) [a]**A**[a]**B**	—	58.6% (40.8; 76.4)	36% (81.5; 91.1)	59.7% (38.6; 78.0)	0.50
Gentamicin **(N = 5674)**	66.9% (63.7; 70.1)	78.1% (76.6; 79.6) [a]**A**[a]**F**	80.0% (77.3; 82.7) [a]**A**[a]**F**	78.6% (75.0; 82.2) [a]**A**[a]**F**	89.7% (78.7; 100.7)	71.0% (69.2; 72.8)	74.3% (67.8; 80.8)	0.71
Meropenem **(N = 5989)**	81.2% (79.5; 82.9)	95.0% (94.2; 95.8) [a]**A**[a]**D**[a]**F**	94.0% (92.4; 95.6) [a]**A**[a]**D**[a]**F**	86.1% (83.1; 89.1)	—	85.9% (84.2; 87.6) [a]**A**	86.9% (75.8; 93.4)	0.85
Ciprofloxacin **(N = 5702)**	33.0% (30.6; 35.4)	30.0% (28.4; 31.7) [a]**D**	37.9% (34.7; 41.1) [a]**B**[a]**D**[a]**F**	22.9% (19.3; 26.6)	48.3% (30.2; 66.4) [a]**D**	27.0% (24.9; 29.1)	24.5% (12.0; 43.7)	0.26
Piperacillin-Tazobactam (N = 4970)	65.0% (63.2; 66.8)	81.0% (79.6; 82.4) [a]**A**	86.9% (84.7; 89.1) [a]**A**[a]**B**[a]**F**	82.0% (78.7; 85.3) [a]**A**	93.1% (83.9; 102.3) [a]**A**	80.0% (77.8; 82.2) [a]**A**	76.7% (59.6; 88.6)	0.71
Cefepime **(N = 4021)**	40.9% (37.7; 44.1)	60.0% (57.9; 62.1) [a]**A**[a]**D**[a]**F**	84.0% (81.6; 86.4) [a]**A**[a]**B**[a]**D**[a]**F**	43.9% (39.7; 48.1)	—	36.0% (32.7; 39.3)	48.1% (27.8; 69.1)	0.48

[a]Results are based on two-sided z-tests with a significance level p <0.05. For pair-wise comparison of susceptibility profile between regions, the region with lower susceptibility (labelled by the bold capital alphabet) is placed within the region, which has significantly higher susceptibility compared to it (i.e. *E. coli* showed a statistically significantly higher susceptibility to fosfomycin in the south region than in the North region). Tests are adjusted for all pairwise comparisons within a row of each innermost sub-table using the bonferroni correction. The 95% confidence interval is provided in parenthesis.

(analyses vs piperacillin/tazobactam breakpoints); that for "carbapenems" is the average of imipenem and meropenem.

Funding

The study was unfunded and relied entirely on the existing infrastructure, manpower, motivation and goodwill.

Results

Antimicrobial susceptibility profile of E. coli across India

Antimicrobial susceptibility profiles of 7790 isolates of community-acquired *E. coli* were analyzed from a total of 51,703 samples received at the outpatient departments surveyed. The overall susceptibility rates across all sites are shown in Table 1, with site-by-site detail in supplementary Table S1 and regional rates, with confidence intervals for major antibiotic groups in Table 2. The regional rates for major oral antibiotics are illustrated by site in Figure 2, with those for intravenous antimicrobial agents in Figure 3, with further detail in Supplementary Table S2.

Antimicrobial susceptibilities at two centers (one in Delhi and another in Gujarat) were considered to be outliers and their data were not included in the national and regional means (Table 1). The center in central India (Bhopal) provided a combined antibiogram for urinary *E. coli* from in- and out-patients and their data, likewise, were excluded when calculating national susceptibility. Significant inter-regional variability in resistance rates was observed for all drugs, as shown in Table 2. The ICC was highest (0.92) for fosfomycin, indicating the least variation, and the lowest (0.26), indicating the most variation, for ciprofloxacin. We reviewed the salient features in the subsequent section by antibiotic or antibiotic class.

Fosfomycin

Across all the six regions, fosfomycin was the most reliably active antimicrobial, with 94% (92-97%) national susceptibility.

Nitrofurantoin

The national susceptibility to nitrofurantoin was 85%. In general, W India had a high susceptibility (88-97%), as did S India (87-95%), whereas a wide variation was observed for sites across N and central India (61-96%).

Co-trimoxazole

Antimicrobial susceptibility to co-trimoxazole was low, ranging from 36% to 68%, with a national rate of 49%. Two individual centers in S India (Bangalore and Thiruvananthapuram) reported 68% susceptibility—the highest in the country.

First- and second-generation cephalosporins

These drugs performed poorly, with only around 26% susceptibility nationally.

Third- and fourth-generation cephalosporins

The susceptibility rates ranged between 40 and 50%, averaging at 46.3% (Table 1, with details in Supplementary Table S1 and S2). Guwahati in the NE had the highest susceptibility rate at 67%, and Patna in E. India had the lowest at 29% (Figure 2). The national susceptibility rate for cefepime was 52%, with local rates ranging from 93% in Surat to 36% at the sole center in Delhi where it was tested.

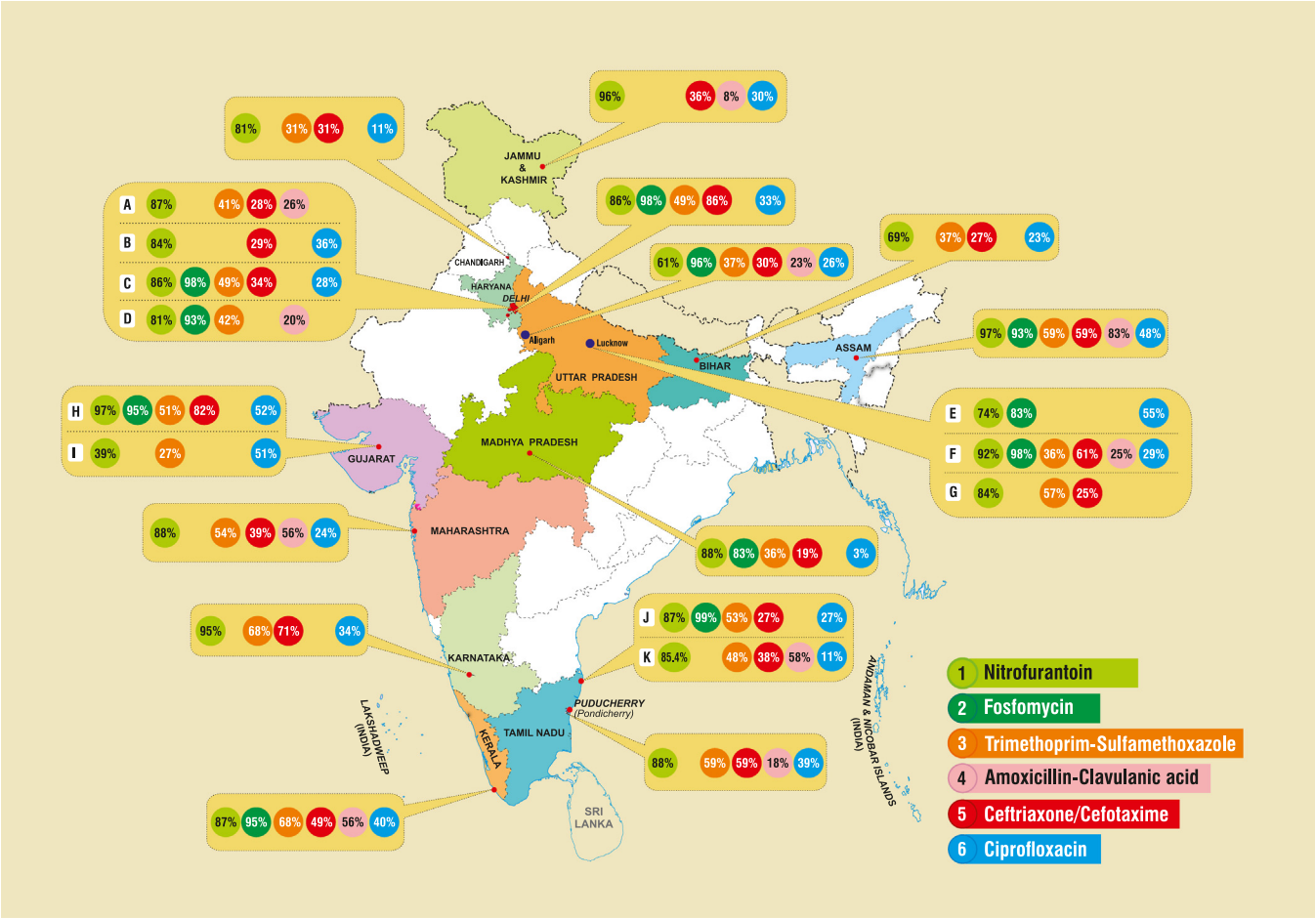

Figure 2. Antimicrobial Susceptibility profile of *Escherichia coli* to the major antibiotic groups. Number of strains tested for each group were as follows: nitrofurantoin (7790), fosfomycin (4165), trimethoprim-sulphamethoxazole (6639), amoxicillin-clavulanic acid (4307), ceftriaxone/cefotaxime (6014), ciprofloxacin (6712).

Estimation of extended-spectrum beta-lactamases prevalence

The national prevalence rate for ESBLs was thereby estimated at 54%, ranging from 33% in NE to 58% in N. India.

β-Lactam/β-lactamase inhibitors

Overall, the susceptibility rates were 81% for piperacillin/tazobactam and 47% for amoxicillin/clavulanic acid; cefoperazone/sulbactam lacked a CLSI break point but if the piperacillin/tazobactam break point was applied, the susceptibility was estimated at 79%. The susceptibility range among sites was extremely wide for amoxicillin/clavulanate, from 6% in one center in Delhi to 83% in Guwahati (Assam). In contrast, the rates for cefoperazone/sulbactam and piperacillin/tazobactam were more narrowly spread, from 72% (Chandigarh) to 92% Thiruvananthapuram, Kerala) for cefoperazone/sulbactam and 81% to 94% in W, NE, and S India to 82% in E India for piperacillin/tazobactam. Lower rates were observed in N India (64%) and Delhi (79%).

Carbapenems

The national susceptibility rates were 88% for imipenem and meropenem (Table 1 and Figure 3). Significantly higher susceptibility rates to meropenem were observed in S (90-98%) and W India (92-95%) than other regions (P <0.05).

There were several outliers: one site in Lucknow had a meropenem susceptibility rate of 68% and one in Bhopal (central India) had a rate of 64%. An extreme outlier in Delhi recorded 42% meropenem susceptibility; this was not included in the calculation of averages.

Fluoroquinolones

The national susceptibility rate for ciprofloxacin was 29%, with only three centers reporting susceptibility rates exceeding 50% (Table 1); fewer centers tested levofloxacin, with only a slightly higher (35%) susceptibility rate recorded.

Aminoglycosides

High rates susceptibility rates were observed to gentamicin (75-84%) and amikacin (88-96%) in S India and in W India (gentamicin: 74-85% and amikacin: 97-98%. The rates by region are given in Figure 3. Two outliers, one in Delhi and another in Gujarat, reported less than 50% susceptibility to amikacin; the Delhi site was the same one that had an unusually low susceptibility to meropenem. Given the frequent genetic linkage of New Delhi metallo-beta-lactamases (NDM)-carbapenemases and aminoglycoside compromising ArmA and Rmt ribosomal methyltransferases, this parallel pattern lends confidence in both the outlying results [8].

Discussion

The rapid emergence and proliferation of multi-drug resistant uropathogens—often harboring ESBLs, AmpC enzymes, and carbapenemases—makes the treatment of even simple UTIs more challenging,

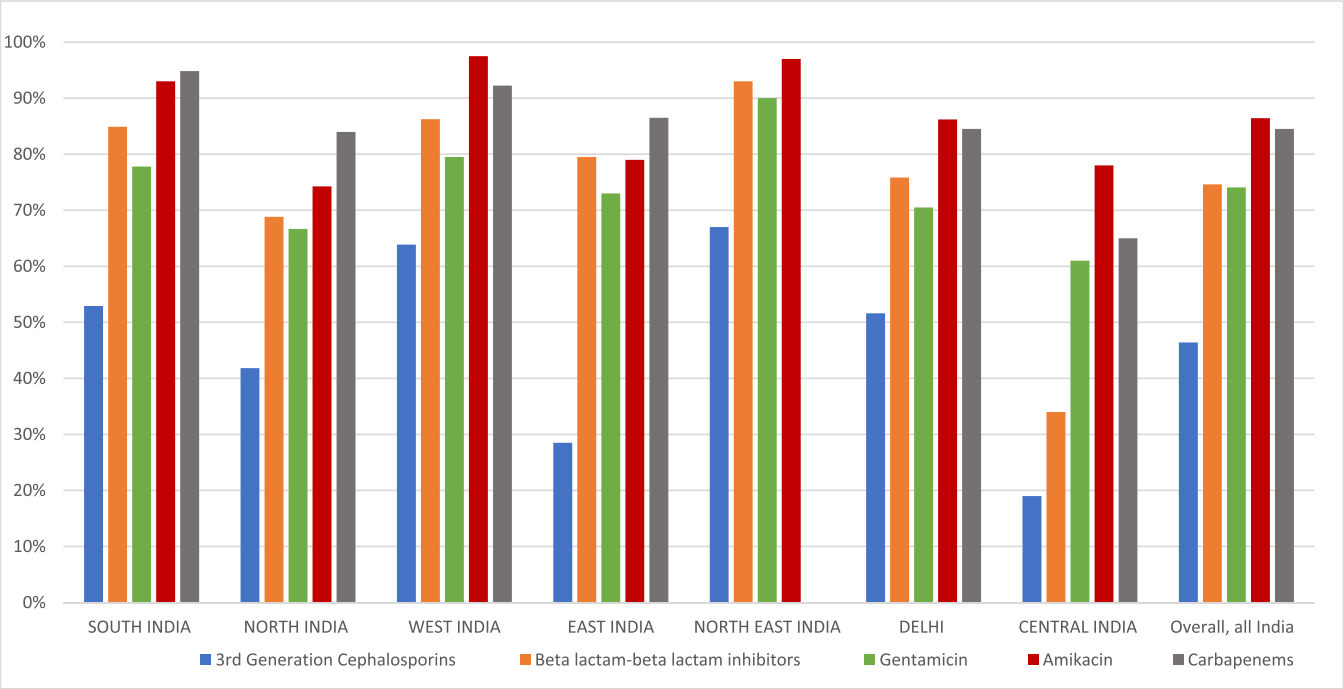

Figure 3. Average susceptibility of *Escherichia coli* to five major antimicrobial groups. Third-generation cephalosporins: average of ceftazidime, cefotaxime, ceftriaxone, and cefixime. β-Lactam-β-lactamase inhibitors: average of piperacillin-tazobactam and cefoperazone/sulbactam. Carbapenems: average of imipenem and meropenem. Number of strains tested were as follows: Third-generation cephalosporins: ceftazidime (3871), cefotaxime (3369), ceftriaxone (2645), and cefixime (530). Beta-Lactam-beta-lactamase inhibitors: piperacillin-tazobactam (5242) and cefoperazone/sulbactam (4094). Aminoglycosides: gentamicin (6834), amikacin (6945) Carbapenems: imipenem (6203) and meropenem (7064).

often rendering empirically used antimicrobials inactive [9]. Providing relevant antibiograms to clinicians is vital to addressing this issue; it is also vital to stratify by whether UTI isolates are from in- or out-patients [10]. The treatment of UTIs in India follows national and international guidelines; however, the large regional variations observed in our study suggest that management should be tailored to reflect local resistance rates [11,12].

E. coli is considerably the most common uropathogen worldwide [13]. Here, we tracked antimicrobial susceptibility among isolates of the species recovered from patients with UTI attending outpatient departments in 22 centers across India. High resistance rates were seen, especially in N India, where many centers (i.e. those in Delhi, Lucknow, Aligarh, and Patna) are located across the Gangetic plains. Two of the outliers, with particularly high resistance rates, lie in this region. As illustrated, for example, by https://vividmaps.com/india-maps/, this region has a burgeoning population, many of whom lack safe water and sanitation and who, quite possibly, experience extensive inappropriate antimicrobial prescribing.

Fosfomycin, with 94% overall susceptibility, emerged as the most reliably active antimicrobial *in vitro*, although with significantly greater susceptibility in S India than in N. India, P <0.05. These findings are consistent with other studies in India, including recently published data from the Odisha State, where susceptibility rates of 99% and 91.3% were recorded for *E. coli and K. pneumoniae*, respectively [14]. Fosfomycin, prescribed as a single oral dose of 3 g, maintains good *in vitro* activity, regardless of the presence of other resistances [15]; however, clinical outcomes in cystitis were reportedly poorer than with a 5-day high-dose (100 mg every 8 hours) course of nitrofurantoin [16]. A complicator is that the standard regimen for nitrofurantoin is 100 mgevery 12 hours and not every 8 hours; moreover, it is plausible that two- or three-dose fosfomycin regimens may be more effective than the licensed single-dose therapy [16]. Advocating the mainstream use of fosfomycin does raise concerns about emergence of resistance, especially because it is a useful salvage drug for infections involving extremely and pan-drug resistant bacteria [17].

Surprising rates of resistance were seen to nitrofurantoin, which shows near 100% activity in surveys of urinary *E. coli* collected in Europe [18]. The overall susceptibility rate was 85% but with rates as low as 61-74% in Aligarh, Patna, and Lucknow, which are widely separated cities across northern India. Susceptibility in W India (93.1%) was significantly greater (P <0.05) than in N, S, or E India or in the Delhi NCR region, whereas susceptibility in NE India was significantly greater than in E India. Perhaps of note, the sites with the lowest susceptibility rates were higher tertiary centers that received more referrals. Other studies have reported susceptibility rates of 90.3% for *E. coli* from N India, 91% for Rajasthan, 94.2% for S India, 93.9% for E India, and 93.4% for W India [13,19]. Mohapatra et al. [13] reported 94.2% susceptibility for *E. coli* from community-acquired UTIs across four centers in different regions of India; however, recent data from Guntur in Andhra Pradesh suggests only 60% susceptibility of *E. coli* to nitrofurantoin in outpatient settings [20]. In the UK, resistance to nitrofurantoin in *E. coli,* although uncommon, is associated with chromosomal mutations [21]. Studies are urgently needed to explore whether these or other modes of resistance have evolved and are accumulating in India.

The resistance rates to other orally administrable antibiotics were very high, suggesting that their empirical use will be associated with frequent failure. Co-trimoxazole retained activity against only 49% of isolates. Bhargava et al. in 2022 [22] reported an even lower susceptibility at 39.8% and Vijayganapathy et al. in 2021 [23] reported 24% susceptibility; their data sets for *E. coli* were from N and S India, respectively. In the pairwise comparisons, isolates from S and W India independently demonstrated greater susceptibility than those from N, E, or central India or from the Delhi NCR (P <0.05).

In the case of fluoroquinolones, data were most complete for ciprofloxacin, with a national susceptibility rate of only 29%. Similar rates were seen for norfloxacin and levofloxacin. The rates for

ciprofloxacin ranged from 11% to 55% in N India, 24-52% in W India, 11-40% in S. India, and 11-36% in Delhi, indicating little clear regional difference despite considerable site-to-site differences within regions, reflected in the low ICC. These results are in keeping with the findings of others: Bharara et al. [24] reported 50% and 33% susceptibility to levofloxacin and ciprofloxacin, respectively, for *E. coli* in Delhi in 2018, whereas, in S India, Vijayganapathy et al. [23] reported 38% and 26% susceptibility, respectively. All these fluoroquinolone rates were lower than the rates for co-trimoxazole and amoxicillin/clavulanic acid. Losada et al. [25] in Spain, likewise, reported greater susceptibility to co-trimoxazole and amoxicillin/clavulanic acid (70% and 77%, respectively) than to fluoroquinolones (67%) for *E. coli*. Given the additional concerns regarding fluoroquinolone safety [26] and their propensity to cause collateral damage to the gut flora, there seems no good reason to still advocate these agents for empirical use in UTIs in India.

Turning to intravenous agents, likely to be used for an ascending UTI, the national susceptibility rate to third-generation cephalosporins was 46.3%, whereas that to cefepime was 52%. W India exhibited significantly greater susceptibility to cefotaxime (85.1%) than other regions, where it varied between 27% and 53% (P <0.05). Similar patterns were seen for ceftazidime, ceftriaxone, and cefepime, with the highest susceptibility observed in W India. Cefepime susceptibility was notably higher in W India at 78-91%. For comparison, Jangid et al. 2021 [9], in a multicentric study spanning many Indian centers, reported 33.6% susceptibility for *E. coli* to cefixime, whereas Bhargava et al. [22] reported less than 10% susceptibility for cefepime in N India. At least one center in each region tested the prevalence of ESBLs directly. Although this is limited coverage, these ESBL data were entirely consistent with cephalosporin resistance data, which were extensive. Such cross-referencing of two data sets adds confidence. Moreover, the similarly high rates of resistance to third-generation cephalosporins and cefepime suggest that most cephalosporin resistance is attributable to ESBLs rather than to AmpC enzymes, although W India, with its higher cefepime susceptibility, may be an exception. An exceptionally high ESBL prevalence (72%) was reported by the site in Patna, Bihar, perhaps reflecting the hospital being a major referral center. Paul et al. [27] previously reported a 26.2% ESBL prevalence in Assam (NE India), whereas Behera et al. [28] reported 43% combined prevalence in *E. coli* and *Klebsiella pneumoniae* from community UTIs from E. India, and, in 2021, Kumar et al. [29] reported a 46.6% ESBL prevalence in *E. coli* from Uttarakhand in N India. In 2022, Mohapatra et al. [13] reported an ESBL prevalence of more than 50% across four centers for *E. coli*. Our observation of higher apparent susceptibility rates to ceftazidime than to cefotaxime (Table 1) suggested that the ESBL-mediated resistance there was due to CTX-M–type ESBLs, although this requires molecular confirmation.

Piperacillin/tazobactam susceptibility was recorded as 81% overall, almost matched by cefoperazone/sulbactam at 79%, whereas amoxicillin/clavulanic acid was active only against 47% of the isolates. Overall, NE India, followed by S, W, and E India exhibited significantly higher susceptibility to piperacillin/tazobactam than N India (P <0.05). Mohapatra et al. [13] 2022 reported similar (75.1%) susceptibility data for piperacillin/tazobactam but much higher susceptibility (74.7%) for amoxicillin/clavulanic acid among Gram-negative uropathogens.

Based on testing at only a few sites, S India reported higher susceptibility (89%) to cefoperazone/sulbactam than to piperacillin/tazobactam (81%), reversing the national pattern, although caution is needed owing to the lack of international break points for the sulbactam combination. Vijayaganapathy et al. [23] reported 80% susceptibility to piperacillin/tazobactam and 78% to cefoperazone/sulbactam for urinary *E. coli* from out-patients in S India, also suggesting the near-equal activity of these combinations.

Nationwide, the susceptibility to aminoglycosides was around 80% (gentamicin, 76%; amikacin, 87%). In S. and W. India, however, amikacin susceptibility rates were as high as 88-96% and 97-98%, respectively, whereas at two centers in N India—in Lucknow and Aligarh—the susceptibility was only at 60%. The S (78.0%), E (78.6%), and W regions (80.0%) recorded significantly higher proportions of susceptibility to gentamicin (P <0.05) than in N India (70%) and Delhi NCR (71.0%). Previously, Bhargava et al. [22] reported 77% susceptibility for amikacin for *E. coli* in N India.

Despite the concerns about the community spread of NDM carbapenemases in India, susceptibility to carbapenems remained at 88% nationally, with high rates reported from S (90-98%) and W India (92-95%) [30]. Similarly, in a four-center study, Mohapatra et al. 2022 reported 90.4% carbapenem susceptibility for *E. coli* [13], whereas Vijayganapathy et al. [23] reported 99% susceptibility in S India and Nair et al. reported 87.8% susceptibility in W India [23,31]. Disturbingly, much lower susceptibility rates were seen at the outlier center in Delhi (42%) and at single centers in Lucknow, N India (68%), and Bhopal (64%). Bhargava et al. [22], likewise, reported low susceptibility for 37.2% for meropenem and 57.4% for imipenem from Allahabad, N India, testing *E. coli* from in- and out-patients.

Based on our results, we recommend nitrofurantoin and fosfomycin as the first-line antibacterial agents for uncomplicated community-acquired UTIs in India. Both these agents have the further benefit of causing little collateral damage to the gut flora [32]. The caveats and cautions are the following: (i) although the susceptibility data favor fosfomycin, trial data indicate that nitrofurantoin may be a more effective agent [16], (ii) several centers reported significant (>20%) rates of resistance to nitrofurantoin and one had only 85.3% susceptibility to fosfomycin, and (iii) neither agent is reliably effective in complicated or ascending infection. For such infections warranting intravenous therapy, aminoglycosides and the more potent β-lactam/β-lactam inhibitor combinations (i.e. piperacillin-tazobactam and cefoperazone-sulbactam) remain widely active, as do carbapenems—although we advocate reserving these where possible. Geographic variability underscores the need to generate and use local antibiograms to support appropriate empirical prescribing, exactly as DASH seeks to support [20]. The higher resistance in N India may be linked to several factors: greater over-the-counter sale of antibiotics, indiscriminate prescription of antibiotics, large population with low per capita income, higher burden of disease, and substandard drugs [33–35]. It also underscores the likely weakness of any global surveillance that only includes three or four centers to represent a country as large and diverse as India.

Limitations

This study used the hospitals' routine data, allowing us to assemble a large amount of geographically representative information without additional testing. The approach does, however, leave the study vulnerable to site-to-site variations in methodology. We sought to control and correct these as much as possible but cannot be certain that they were completely eliminated. As with almost all studies of community UTIs, the study is likely to be subject to the problem that microbiological sampling is skewed toward complicated, unresponsive, and recurrent cases that are more likely to have resistant pathogens [36]. Moreover, because most primary and secondary care hospitals do little or no culture and susceptibility testing from urines, we were obliged to largely use tertiary centers and, even at their outpatient departments, these may serve a more complex patient population, more likely to harbor resistant pathogens.

Conclusion

Because antibiotic susceptibility rates vary strikingly across a large country such as India, local antibiograms should guide empirical treatment for simple UTIs. India is a large, diverse country, with large variations in population, per capita income, and literacy. The variations extend to health care infrastructure, adoption of best practices, and antimicrobial resistance. W and S India are more prosperous and are less densely populated than N India, with better health care infrastructure and wider scale adoption of best practices, including judicious

use of antimicrobials. Maybe these important indicators are being reflected in the significant variations in resistance observed in different regions of India. This study confirms that fosfomycin and nitrofurantoin remain excellent oral empirical choices for uncomplicated community UTIs due to *E. coli* in India, including when these are due to strains resistant to other agents. Nitrofurantoin and fosfomycin have the further benefit of causing little collateral damage to the gut flora. Nonetheless, notably raised rates of resistance to nitrofurantoin were recorded at several sites and for fosfomycin at one site. Such data need to be considered alongside the trial showing better outcomes for nitrofurantoin [16]. Our findings strongly discourage the empirical use of fluoroquinolones and third-generation cephalosporins in simple cystitis. β-lactam/β-lactamase inhibitor combinations and aminoglycosides likely remain the best carbapenem-sparing agents, where ascending infection demands intravenous therapy.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

MR contributed to the conceptualization of the study, analysis, drafting and editing of the manuscript; AG,AS,AJ, BM, BGS, FK, JBK, MJ, NPS, RG, SM, SF, SP, MSJ, VRYD, NG, and MS participated in the study and shared the data; MR, AHS, HS, ID, VRYD, KM, SM, and SD drafted and edited the manuscript; MR, RAZ, DL, AHS, AP, IP, RK, and HS analyzed the data; SJ, RR, SM, SD, BL, KAB, KMD, RK, ZAJ, SS, SS, NT, KHSJ, RS, PK, AAR, RS, ABK, and DML supervised and gave intellectual input; and KAB, KM, and SJ did the statistical analysis.

Data sharing statement

Data supporting the findings of this study are available.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2024.100370.

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