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

Background: Evidence-based prescribing is essential to optimise patient outcomes in cystitis. This requires knowledge of local antibiotic resistance rates. *DASH to Protect Antibiotics* (https://dashuti.com/) is a multicentric mentorship programme guiding centres in preparing, analysing and disseminating local antibiograms to promote antimicrobial stewardship in community UTI. Here we map the susceptibility profile of *Escherichia coli* from 22 Indian centres. **Methods:** These centres spanned 10 Indian States and three Union Territories. Antibiograms for urinary *E. coli* from the outpatient departments were collated. Standardisation was achieved by regional online training; anomalies were resolved via consultation with study experts. Data were collated and analysed. **Findings:** Nationally, fosfomycin, with 94% susceptibility (inter-centre range 83-97%), and nitrofurantoin with 85% susceptibility (61-97%) retained widest activity. Susceptibility rates were lower for co-trimoxazole (49%), fluoroquinolones (31%) and oral cephalosporins (26%). Rates for third- and fourth- generation cephalosporins were 46% and 52%, respectively, with 54% (33-58%) ESBL prevalence. Piperacillin-tazobactam (81%) amikacin (88%), meropenem (88%) retained better activity, but one centre in Delhi recorded only 42% meropenem susceptibility. Susceptibility rates were mostly higher in South, West and Northeast India; centres 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.

Interpretation: Fosfomycin and nitrofurantoin are the preferred oral empirical choices for uncomplicated *E. coli* cystitis in India, though 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 globally in both community- and hospital-acquired settings [3]. Increasing resistance complicates treatment, making outcomes uncertain, even in simple cystitis [4].

Minimising 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 *DASH to Protect Antibiotics* (https://dashuti.com/).

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

METHODS

Centre recruitment

This ongoing study was open to all interested centres across India, including public and private medical colleges, tertiary healthcare facilities and standalone laboratories. Invitations to participate were sent by email, WhatsApp and through LinkedIn. Forty-one centres were approached, of which 29 (27 tertiary-care public and private hospitals and two private laboratories) agreed to join.

Five hospitals and both 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 neighbouring 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), three in West (W) India (two in Gujarat and one in Mumbai), along with single centres 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 National Capital Region) were analysed 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 3 sites) and Patna. Seventeen centres were academic whereas five were non-academic. Ten states and three union territories participated. The duration of this study was one year, from 1st January 2022 to 31st December 2022.

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

Initial actions to achieve standardisation of methods

Prior to preparing the Outpatient Department (OPD)-based antibiograms, a workshop on implementation of the WHONET and BACLINK susceptibility data analysis software (https://whonet.org) was conducted by three centres [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 . Centres 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 screened by visual examination of urine turbidity. Twelve centres used automated bacterial identification for putatively-infected urines; 10 used classical manual methods [5]. Antimicrobial Susceptibility testing (AST) was performed according to CLSI guidelines M100-Ed33) 2022 [6]. Ten sites largely used disc diffusion testing whereas 12 used automated systems, six used a mixture of both approaches. Quality control was practiced by all laboratories. ESBLs were detected using cephalosporin/clavulanic acid synergy tests by eight centres.

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

Data collection, handling, review and validation

Only clinical isolates from patients presenting with a symptomatic UTI at an out-patient 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 analyse 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. 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. Arithmetic and harmonic means were calculated to average percentage susceptibility rates reported by different sites. Since percent susceptibilities are ratios, harmonic means were preferred; however, results were similar regardless of which type of average was used (see 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/β-lactamase inhibitors' is for piperacillin/tazobactam and cefoperazone/sulbactam (analysed *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 analysed from a total of 51,703 samples received at the OPDs surveyed. 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. Regional rates for major oral antibiotics are illustrated by site in Figure 2, with those for i.v. antimicrobial agents in Figure 3, with further detail in Supplementary Table S2.

Antimicrobial susceptibilities at two centres (one in Delhi, another in Gujarat) were considered to be outliers and their data were not included in the national and regional means (Table 1); The centre in Central India (Bhopal) provided a combined antibiogram for urinary *E. coli* from both 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 least variation, and lowest (0.26), indicating most variation, for ciprofloxacin. We review the salient features below, by antibiotic or antibiotic class.

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

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

Co-trimoxazole: Antimicrobial susceptibility to co-trimoxazole was low, ranging from 36% to 68%, with a national rate of 49%. Two individual centres 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: Susceptibility rates ranged between 40 and 50%, averaging 46.3%. (Table 1, with details in Supplementary Table S1and S2). Guwahati in the NE had the highest susceptibility rate, at 67%, and Patna in E. India 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 centre in Delhi where it was tested.

Estimation of ESBL 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, susceptibility rates were 81% for piperacillin/tazobactam and 47% for amoxicillin/clavulanic acid; cefoperazone/sulbactam lacks at CLSI breakpoint but, if the piperacillin/tazobactam breakpoint was applied, susceptibility was estimated at 79%. The susceptibility range among sites was extremely wide for amoxicillin/clavulanate, from 6% in one centre in Delhi to 83% in Guwahati (Assam). By contrast, 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 from N. India (64%) and Delhi (79%).

Carbapenems: National susceptibility rates were 88% for both imipenem and meropenem (Table 1 and Figure 3). Significantly higher susceptibility rates to meropenem were observed in S. (90 to 98%) and W. India (92 to 95%) compared with other regions ($p<0.05$).

There were several outliers: one site in Lucknow had a meropenem susceptibility rate of 68%, 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 centres reporting susceptibility rates exceeding 50% (Table 1); fewer centres tested levofloxacin, with only a slightly higher (35%) susceptibility rate recorded.

Aminoglycosides: High rates susceptibility rates were observed to gentamicin (75 to 84%) and amikacin (88 to 96%) in S. India and also in W. India (gentamicin: 74 to 85% and amikacin: 97 to 98%. 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 unusually low susceptibility to meropenem. Given the frequent genetic linkage of metallo (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 harbouring ESBLs, AmpC enzymes and carbapenemases – makes the treatment of even simple UTIs more challenging, often rendering empirically-used antimicrobials inactive [9]. Providing relevant antibiograms to clinicians is vital to addressing this issue; it is vital also to stratify by whether UTI isolates are from in- or out- patients [10]. Treatment of UTIs in India follows national and international guidelines, but 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 commonest uropathogen worldwide [13]. Here we tracked antimicrobial susceptibility among isolates of the species recovered from patients with UTI attending outpatient departments in 22 centres across India. High resistance rates were seen, especially in N. India, where many centres (i.e., those in Delhi, Lucknow, Aligarh, Patna) are located across the 'Gangetic Plains'. Two of the outliers, with particularly high resistance rates, lie in this region. As illustrated e.g., 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*, though with significantly greater susceptibility in S. compared with 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 grams, maintains good in-vitro activity regardless of the presence of other resistances [15]; however clinical outcomes in cystitis were reportedly poorer than with a five-day high-dose (100 mg q8h) course of nitrofurantoin [16]. A complicator is that the standard regimen for nitrofurantoin is 100 mg q12h, not q8h; moreover, it is plausible that two- or three- dose fosfomycin regimens may be more effective than the licensed single-dose therapy [16]. Advocating mainstream use of fosfomycin does raise concerns about emergence of resistance, especially as 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 to 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, while susceptibility in NE India was significantly greater than in E. India Perhaps of note, the sites with the lowest susceptibility rates were higher tertiary centres, receiving 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 centres 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,* though uncommon, is associated with chromosomal mutations [21]. Work is urgently needed to explore whether these or other modes of resistance have evolved and are accumulating in India.

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 even lower susceptibility, at 39.8%, and Vijayganapathy *et al.* in 2021 [23] reported 24% susceptibility; their datasets for *E. coli* were from N. and S. India respectively. In pairwise comparisons, isolates from S. and W.

India independently demonstrated greater susceptibility compared with 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. Rates for ciprofloxacin ranged from 11 to 55% in N. India, 24 to 52% in W. India, 11 to 40% in S. India and 11 to 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 whilst, in S. India, Vijayganapathy *et al.* [23] reported 38% and 26% susceptibility, respectively. All these fluoroquinolone rates were lower than 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 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%, whilst that to cefepime was 52%. W. India exhibited significantly greater susceptibility to cefotaxime (85.1%) compared with 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 to 91%. For comparison, Jangid *et al.* 2021 [9], in a multicentric study spanning many Indian centres, reported 33.6% susceptibility for *E. coli* to cefixime, while Bhargava *at al.,* 2022 [22] reported less than10% susceptibility for cefepime in

N. India. At least one centre in each region tested prevalence of ESBLs directly. Whilst 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, though 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 centre. Paul *et al.* 2021 [27] previously reported 26.2% ESBL prevalence in Assam (NE. India) whilst Behera *et al.* 2022 [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 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 centres in *E. coli*. Our observation of higher apparent susceptibility rates to ceftazidime than to cefotaxime (Table 1) suggested that much 'ESBL-mediated resistance' there was due to CTX-M type ESBLs, though 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 compared to N. India ($p<0.05$). Mohapatra *et. al.* 2022 reported similar (75.1%) susceptibility data for piperacillin/tazobactam but much higher susceptibility (74.7%) for amoxicillin/clavulanic acid among Gram-negative uropathogens [13].

Based upon testing at only a few sites, S. India reported higher susceptibility (89%) to cefoperazone/sulbactam than to piperacillin/tazobactam (81%), reversing the national pattern, though caution is needed owing to the lack of international breakpoints for the sulbactam combination. Vijayaganapathy *et al.* 2018 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 [23].

Nationwide, susceptibility to aminoglycosides was around 80% (gentamicin, 76%; amikacin, 87%). In S. and W. India, however, amikacin susceptibility rates were as high as 88 to 96% and 97 to 98%, respectively, whereas at two centres in N. India – in Lucknow and Aligarh – susceptibility was only *c.* 60%. The S. (78.0%); E. (78.6%) and W. Regions (80.0%) recorded significantly higher proportion of susceptibility to gentamicin ($p<0.05$) than in N. India (70%) and Delhi NCR (71.0%). Previously, Bhargava *et al.* 2022 reported 77% susceptibility for amikacin among *E. coli* from N. India [22].

Despite concerns about the community spread of NDM carbapenemases in India, susceptibility to carbapenems remained at 88% nationally, with high rates reported from S. (90 to 98%) and W. India (92 to 95%) (30). Similarly, in a four-centre study, Mohapatra *et al*, 2022 reported 90.4% carbapenem susceptibility for *E. coli* [13] whilst Vijayganapathy *et al.* 2018 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 centre in Delhi (42%), and at single centres in Lucknow, N. India (68%), and Bhopal (64%). Bhargava *et al.* likewise reported low susceptibility for 37.2% for meropenem and 57.4% for imipenem from Allahabad, N. India, testing *E. coli* from both in- and out- patients [22].

On the basis of our results, we recommend nitrofurantoin and fosfomycin as 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]. Caveats and cautions are: (i) whereas the susceptibility data favour fosfomycin, trial data indicate nitrofurantoin may be a more effective agent;[16] (ii) several centres 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, both aminoglycosides and the more potent β-lactam/β-lactam inhibitor combinations (i.e., piperacillin-tazobactam and cefoperazone-sulbactam) remain widely active, as do carbapenems – though we advocate reserving these where possible. Geographic variability underscores the need to generate and utilise 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 [33,34,35]. It also underscores the likely weakness of any global surveillance that only includes three or four centres to 'represent' a country as large and diverse as India.

Limitations

This study used 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 towards complicated, unresponsive and recurrent cases, who 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 centres and, even at their outpatient departments, these may serve a more complex patient population, more likely to harbour resistant pathogens.

Conclusions

As antibiotic susceptibility rates vary strikingly across a large country like India, local antibiograms should guide empirical treatment for simple UTIs. India is a large, diverse country with large variations in population, per capita income, literacy. The variations extend to healthcare infra-structure, adoption of best practices and also antimicrobial resistance. W. and S. India are more prosperous and are less densely populated than N. India, with better healthcare infra-structure 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. Both 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 i.v. therapy.

Contributors: 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, MS, participated in the study and shared the data and MR, AHS, HS, ID, VRYD, KM, SM, SD, drafted and edited the manuscript; MR, RAZ, DL, AHS, AP, IP, RK, HS, analysed the data and SJ, RR, SM, SD, BL, KAB, KMD, RK, ZAJ, SS, SS, NT, KHSJ, RS, PK, AAR, RS, ABK, DML supervision and intellectual input; KAB, KM, SJ did statistical analysis

Data sharing statement

Data supporting the findings of this study is available.

Conflict of Interest: None to declare

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Legends

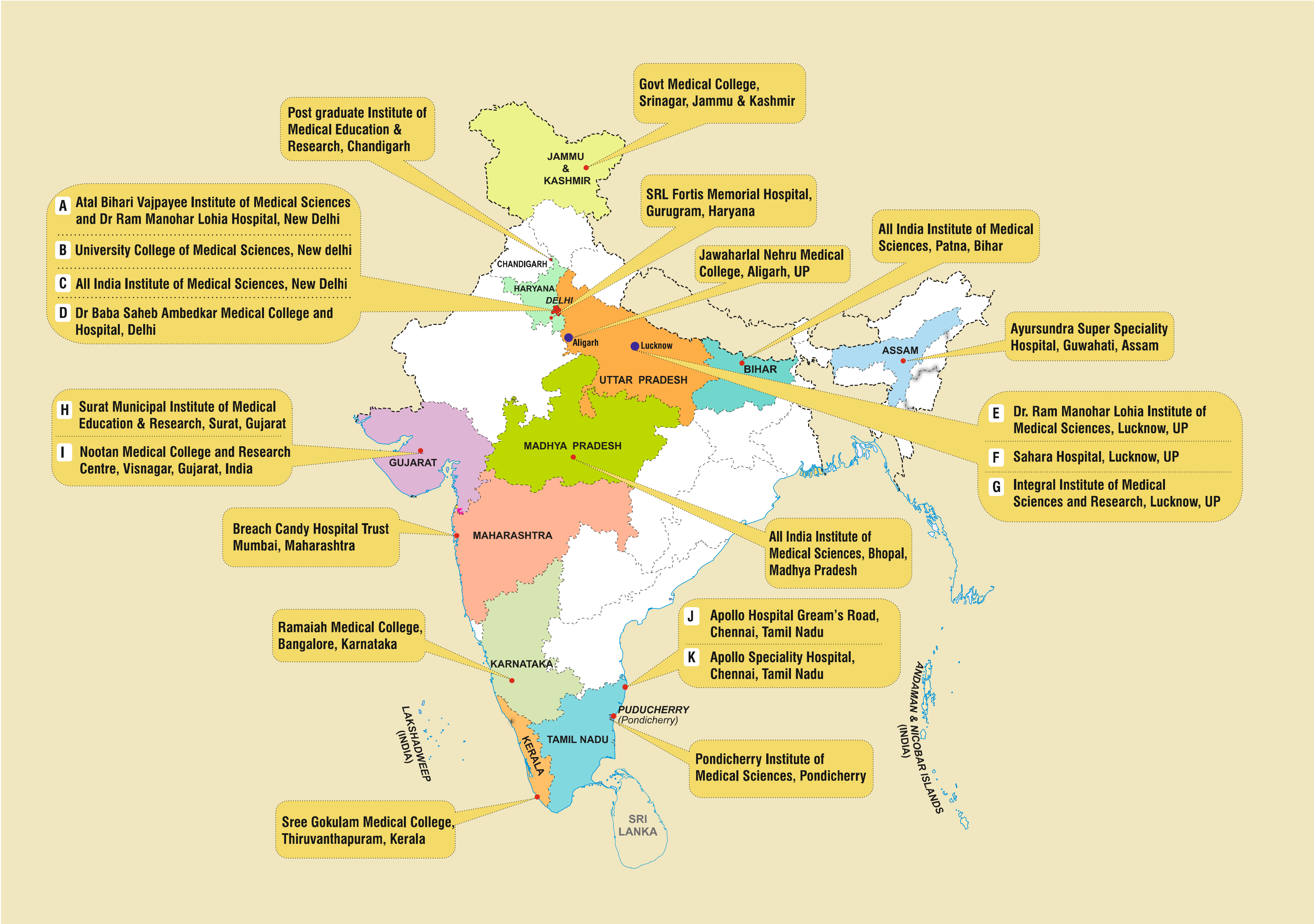
Figure 1: Participating States and Centres

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)

Figure 3: Average susceptibility of *Escherichia coli* to five major antimicrobial groups.

Figure 4: Estimated regional prevalence of ESBLs and carbapenem resistance

Figure 1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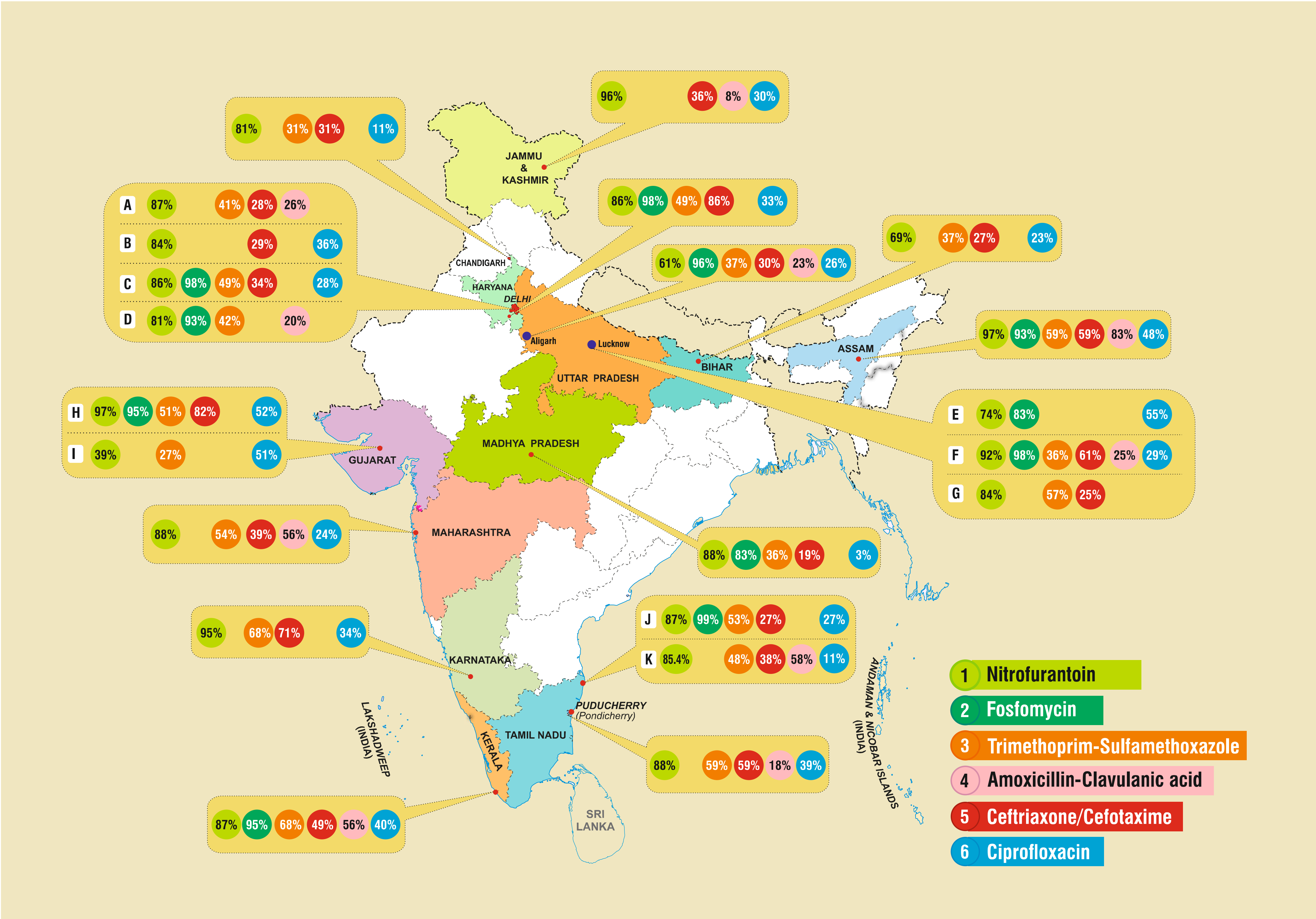
Post graduate Institute of Medical Education & Research, Chandigarh
A Atal Bihari Vajpayee Institute of Medical Sciences and Dr Ram Manohar Lohia Hospital, New Delhi
B University College of Medical Sciences, New delhi
C All India Institute of Medical Sciences, New Delhi
D Dr Baba Saheb Ambedkar Medical College and Hospital, Delhi
SRL Fortis Memorial Hospital, Gurugram, Haryana
Jawaharlal Nehru Medical College, Aligarh, UP
All India Institute of Medical Sciences, Patna, Bihar
Ayursundra Super Speciality Hospital, Guwahati, Assam
E Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP
F Sahara Hospital, Lucknow, UP
G Integral Institute of Medical Sciences and Research, Lucknow, UP
H Surat Municipal Institute of Medical Education & Research, Surat, Gujarat
I Nootan Medical College and Research Centre, Visnagar, Gujarat, India
Breach Candy Hospital Trust Mumbai, Maharashtra
All India Institute of Medical Sciences, Bhopal, Madhya Pradesh
Ramaiah Medical College, Bangalore, Karnataka
J Apollo Hospital Gream's Road, Chennai, Tamil Nadu
K Apollo Speciality Hospital, Chennai, Tamil Nadu
Pondicherry Institute of Medical Sciences, Pondicherry
Sree Gokulam Medical College, Thiruvanthapuram, Kerala
JAMMU & KASHMIR
CHANDIGARH
HARYANA
DELHI
Aligarh
Lucknow
UTTAR PRADESH
BIHAR
ASSAM
GUJARAT
MADHYA PRADESH
MAHARASHTRA
KARNATAKA
PUDUCHERRY (Pondicherry)
TAMIL NADU
KERALA
LAKSHADWEEP (INDIA)
ANDAMAN & NICOBAR ISLANDS (INDIA)
SRI LANKA

Figure 2


JAMMU & KASHMIR
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81% 31% 31% 11%
CHANDIGARH
HARYANA
DELHI
A 87% 41% 28% 26%
B 84% 29% 36%
C 86% 98% 49% 34% 28%
D 81% 93% 42% 20%
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61% 96% 37% 30% 23% 26%
Aligarh
Lucknow
UTTAR PRADESH
69% 37% 27% 23%
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ASSAM
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E 74% 83% 55%
F 92% 98% 36% 61% 25% 29%
G 84% 57% 25%
H 97% 95% 51% 82% 52%
I 39% 27% 51%
GUJARAT
MADHYA PRADESH
88% 83% 36% 19% 3%
MAHARASHTRA
88% 54% 39% 56% 24%
KARNATAKA
95% 68% 71% 34%
J 87% 99% 53% 27% 27%
K 85.4% 48% 38% 58% 11%
PUDUCHERRY
(Pondicherry)
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TAMIL NADU
KERALA
87% 95% 68% 49% 56% 40%
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(INDIA)
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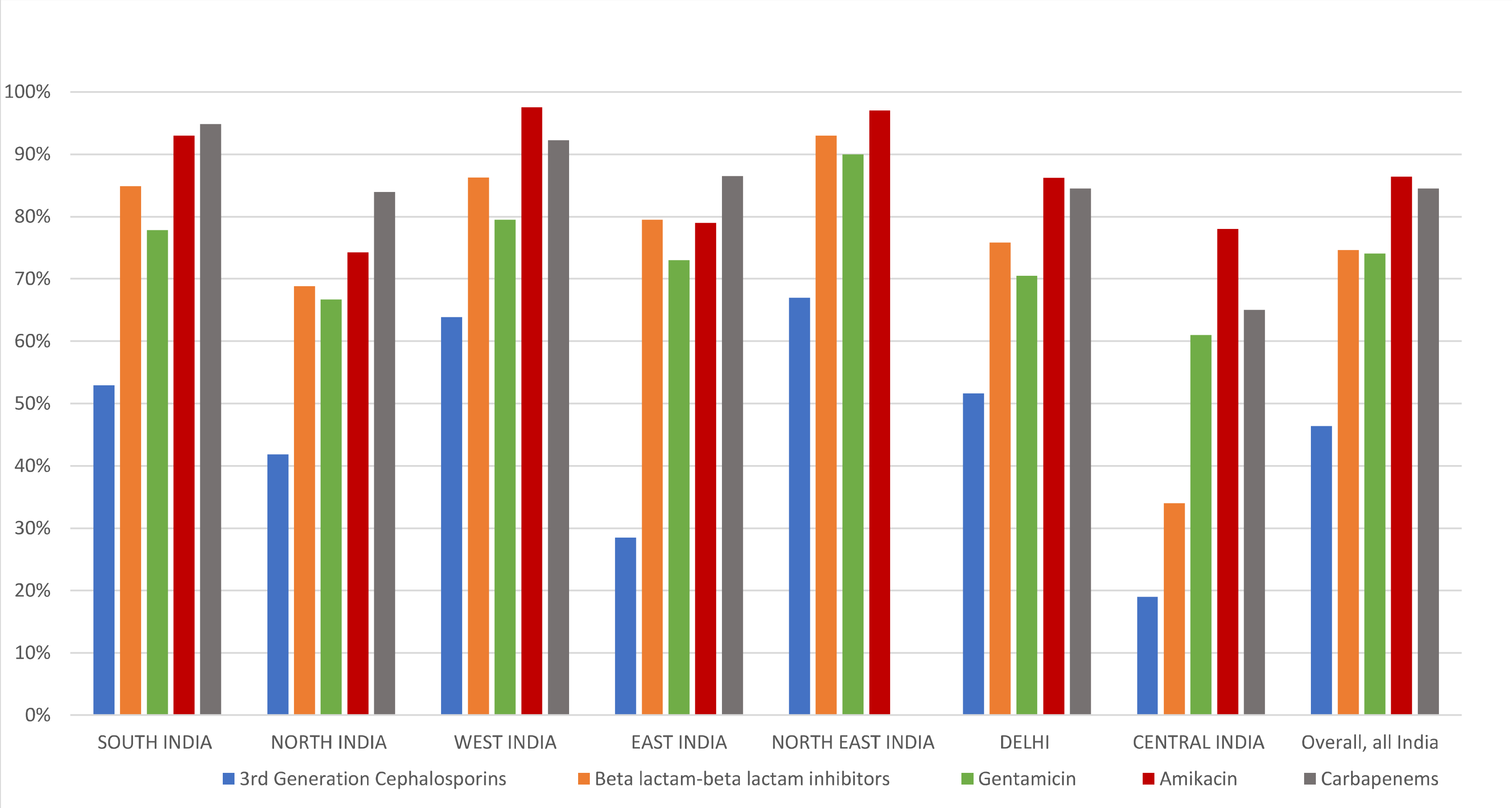
(INDIA)
SRI LANKA
1 Nitrofurantoin
2 Fosfomycin
3 Trimethoprim-Sulfamethoxazole
4 Amoxicillin-Clavulanic acid
5 Ceftriaxone/Cefotaxime
6 Ciprofloxacin

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)

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

					Resistance rates across different centres			
Total no. centres = 22	**No. of centres testing the drug**	**% of centres 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% C.I., 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	ICC
Fosfomycin (N=3187)	92.0% (90.5; 93.5)	97.0% (92.3; 97.7) ***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) ***D**	88.0% (86.8; 89.2) ***A *D**	93.1% (91.4; 94.8) ***A*B*D*F**	69.0% (64.9; 73.0)	96.6% (90.0; 103.2) ***D**	86.7% (85.4; 88.0) ***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*C*D*F**	52.0% (46.7; 55.3) ***A*D*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) ***B*D*F**	39.9% (38.0; 41.7) ***D*F**	85.1% (77.7; 92.4) ***A*B*D*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**	61.1% (58.2; 64.1) ***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*F**	80.0% (77.3; 82.7) ***A*F**	78.6% (75.0; 82.2) ***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*D*F**	94.0% (92.4; 95.6) ***A*D*F**	86.1% (83.1; 89.1)	---	85.9% (84.2; 87.6) ***A**	86.9% (75.8; 93.4)	0.85
Ciprofloxacin (N=5702)	33.0% (30.6; 35.4)	30.0% (28.4; 31.7) ***D**	37.9% (34.7; 41.1) ***B*D*F**	22.9% (19.3; 26.6)	48.3% (30.2; 66.4) ***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**	86.9% (84.7; 89.1) ***A*B*F**	82.0% (78.7; 85.3) ***A**	93.1% (83.9; 102.3) ***A**	80.0% (77.8; 82.2) ***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*D*F**	84.0% (81.6; 86.4) ***A*B*D*F**	43.9% (39.7; 48.1)	---	36.0% (32.7; 39.3)	48.1% (27.8; 69.1)	0.48

* 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. 95% confidence interval is provided in parenthesis.

Supplementary Table S1: Detailed analysis of antimicrobial susceptibility profile of *Escherichia coli* across India

	E.coli	Total	Nitrofurantoin	Fosfomycin	Trimethoprim-Sulfamethoxazole	Ampicillin	Cefazolin	Cefuroxime	Cefoxitin	Ceftazidime	Cefotaxime	Ceftriaxone	Cefixime	Cefepime	Gentamicin	Amikacin	Norfloxacin	Levofloxacin	Ciprofloxacin	Ampicillin-Sulbactam	Amoxicillin-Clavulanic acid	Piperacillin-Tazobactam	Cefoperazone/ sulbactam	Imipenem	Meropenem	Colistin	Cefoperazone
South India: Pondicherry, Tamil Nadu, Karnataka, Kerala	**Pondicherry Institute of Medical Sciences, Pondicherry**	374	88%	-	59%	23%	-	20%	-	-	41%	53%	-	-	75%	-	58%	50%	39%	-	-	74%	-	97%	95%		-
	Sree Gokulam Medical College, Thiruvanthapuram, Kerala	140	87%	95%	68%	30%	-	48%	-	-	-	49%	68%	78%	84%	88%	-	-	40%	-	56%	92%	92%	98%	98%		-
	Ramaiah Medical College, Bangalore, Karnataka	173	95%	-	68%	17%	30%	38%	-	71%	-	-	-		75%	93%	42%	-	34%	-	-	76%	-	90%	90%		-
	Apollo Hospital Gream's Road, Chennai, Tamil Nadu	1153	87%	99%	53%	-	-	-	-	-	38%	-	-	55%	79%	96%	27%	-	27%	-	-	81%	86%	93%	93%	99%	
	Apollo Speciality Hospital, Chennai, Tamil Nadu	106	85%	-	48%	26%	-	25%	-	44%	-	38%	-	51%	76%	95%	-	13%	11%	-	58%	81%	-	97%	97%		
	Average		88%	97%	59%	24%	30%	33%		58%	40%	47%	68%	61%	78%	93%	42%	32%	30%		57%	81%	89%	95%	95%	99%	
	Geometric mean		88%	97%	59%	23%	30%	31%		56%	39%	46%	68%	60%	78%	93%	40%	25%	28%		57%	81%	89%	95%	95%	99%	
	Harmonic mean		88%	97%	58%	23%	30%	29%		54%	39%	46%	68%	59%	78%	93%	38%	21%	24%		57%	80%	89%	95%	95%	99%	
	Total isolates tested		1946	1293	1946	793	173	793		279	1527	620	140	1399	1946	1572	1700	480	1946		246	1946	1293	1946	1946	1153	
North India: Uttar Pradesh and Jammu & Kashmir	**Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP**	451	74%	83%	-	-	14%	-	49%	37%	-	-	-	34%	53%	66%	-	53%	55%	26%	-	61%	-	74%	68%		
	SAHARA Hospital, Lucknow, UP	178	92%	98%	36%	18%	-	19%	-	61%	53%	61%	-	54%	70%	87%	-	-	16%	-	25%	57%	-	90%	89%		

	Integral Institute of Medical Sciences and Research, Lucknow, UP	112	84%	-	57%	-	25%	-	-	32%	-	25%	-	35%	77%	89%	-	-	29%	51%	-	76%	-	89%	89%		
	Govt Medical College, Srinagar, Jammu & Kashmir	471	96%	-	-	2%	-	-	-	-	-	36%					26%	19%	30%		8%		73%		80%		
	Jawaharlal Nehru Medical College, Aligarh	303	61%	96%	37%							30%	33%			55%	24%				23%				92%		
	Average		81%	92%	43%	10%	20%	19%	49%	43%	53%	38%	33%	41%	67%	74%	25%	36%	33%	39%	19%	65%	73%	84%	84%		
	Geometric mean		80%	92%	42%	6%	19%	19%	49%	42%	53%	36%	33%	40%	66%	73%	25%	32%	30%	36%	17%	64%	73%	84%	83%		
	Harmonic mean		79%	92%	41%	4%	18%	19%	49%	40%	53%	34%	33%	39%	65%	71%	25%	28%	27%	34%	14%	64%	73%	84%	83%		
	Total isolates tested		1515	932	593	649	563	178	451	741	178	1064	303	741	741	1044	774	922	1212	563	952	741	471	741	1515		
West India: Gujarat and Maharashtra	**Breach Candy Trust Hospital, Mumbai, Maharashtra**	663	88%		54%	21%		29%				39%		78%	85%	97%			24%		56%	81%	85%	91%	92%	99%	
	Surat Municipal Institute of Medical Education & Research, Surat, Gujarat	87	97%	95%	51%	18%	29%	32%	33%	87%	85%	82%	23%	91%	74%	98%		61%	52%	23%		94%			95%		
	Average		93%	95%	53%	20%	29%	31%	33%	87%	85%	61%	23%	85%	80%	98%		61%	38%	23%	56%	88%	85%	91%	94%	99%	
	Geometric mean		92%	95%	52%	19%	29%	30%	33%	87%	85%	57%	23%	84%	79%	97%		61%	35%	23%	56%	87%	85%	91%	93%	99%	
	Harmonic mean		92%	95%	52%	19%	29%	30%	33%	87%	85%	53%	23%	84%	79%	97%		61%	33%	23%	56%	87%	85%	91%	93%	99%	
(Outlier)	**Nootan Medical College and Research Centre, Visnagar, Gujarat, India**	33	39%		27%						3%				36%	36%	90%		51%	9%		3%					
	Total isolates tested		783	87	783	750	87	750	87	87	120	750	87	750	783	783	33	87	783	120	663	783	663	663	750	663	
East India: Bihar	**All India Institute of Medical Sciences, Patna, Bihar**	467	69%		37%	11%		21%		30%	27%			44%	73%	79%	28%		23%			82%	77%	87%	86%		
	Average		69%		37%	11%		21%		30%	27%			44%	73%	79%	28%		23%			82%	77%	87%	86%		
	Geometric mean		69%		37%	11%		21%		30%	27%			44%	73%	79%	28%		23%			82%	77%	87%	86%		

	Harmonic mean		69%		37%	11%		21%		30%	27%			44%	73%	79%	28%		23%			82%	77%	87%	86%		
	Total isolates tested		467		467	467		467		467	467			467	467	467	467		467			467	467	467	467		
North East India: Assam	**Ayursundra Super Speciality Hospital, Guwahati, Assam**	29	97%	93%	59%	45%				75%		59%			90%	97%			48%		83%	93%					
	Average		97%	93%	59%	45%				75%		59%			90%	97%			48%		83%	93%					
	Geometric mean		97%	93%	59%	45%				75%		59%			90%	97%			48%		83%	93%					
	Harmonic mean		97%	93%	59%	45%				75%		59%			90%	97%			48%		83%	93%					
	Total isolates tested		29	29	29	29				29		29			29	29			29		29	29					
Delhi, Haryana, Chandigarh	**Atal Bihari Vajpayee Institute of Medical Sciences and Dr Ram Manohar Lohia Hospital, New Delhi**	626	87%		41%					45%	28%				67%	74%					25%	68%		74%	72%		
	University College of Medical Sciences, New delhi	229	84%								29%				81%	91%	25%		36%			88%		74%	93%		
	SRL Fortis Memorial Hospital, Gurugram, Haryana	182	86%	98%	49%							36%				94%		40%	33%			83%		93%	92%	99%	
	All India Institute of Medical Sciences, New Delhi	664	84%	93%	42%	16%				34%				36%	74%	88%		27%	28%		20%						
	Post graduate Institute of Medical Education & Research, Chandigarh	222	81%		31%						31%				60%	84%	16%		11%				72%	90%	88%	1%	18%
	Average		84%	96%	41%	16%				40%	29%	86%		36%	71%	86%	21%	34%	27%		23%	80%	72%	83%	86%	50%	18%
	Geometric mean		84%	95%	40%	16%				39%	29%	86%		36%	70%	86%	20%	33%	25%		22%	79%	72%	82%	86%	10%	18%
	Harmonic mean		84%	95%	40%	16%				39%	29%	86%		36%	70%	86%	20%	32%	22%		22%	79%	72%	82%	85%	2%	18%
(Outlier)	**Dr Baba Saheb Ambedkar Medical College and Hospital, Delhi**	149	76%		31%										59%	42%					6%			35%	42%		
	Total isolates tested		2072	846	1843	664				1290	1077	182		664	1890	2072	451	846	1297		1439	1037	222	1408	1408	404	222

Central India: Madhya Pradesh (Outlier)	**All India Institute of Medical Sciences, Bhopal, Madhya Pradesh**	978	88%	83%	36%			13%		19%				21%	61%	78%		6%	3%		18%	32%	36%	66%	64%		
	Average		88%	83%	36%			13%		19%				21%	61%	78%		6%	3%		18%	32%	36%	66%	64%		
	Total isolates tested		978	978	978			978		978				978	978	978		978	978		978	978	978	978	978		

Key:	
>90%	
81-90%	
71-80%	
61-70%	
40-60%	
<40%	

Supplementary Table S2. Antimicrobial susceptibility rates for urinary *Escherichia coli*, by region

	Harmonic Mean and range	Nitrofurantoin	Fosfomycin	Cotrimoxazole	Ampicillin	Cefazolin	Cefuroxime	Cefoxitin	Ceftazidime	Cefotaxime	Ceftriaxone	Cefixime	Cefepime	Gentamicin	Amikacin	Norfloxacin	Levofloxacin	Ciprofloxacin	Ampicillin - Sulbactam	Amoxicillin - Clavulanic Acid	Piperacillin - tazobactam	Cefoperazone/sulbactam	Imipenem	Meropenem	Colistin
SOUTH INDIA	Mean	88	97	59	24	30	33	-	58	40	47	68	61	78	93	42	32	30	-	57	81	89	95	95	99
	range	87 - 95	95 - 99	48 - 68	17 - 30	30	20 - 48	-	44 - 71	38 - 41	38 - 53	68	51 - 78	75 - 84	88 - 96	27 - 58	13 - 50	11 - 40	-	56 - 58	74 - 92	86 - 92	90 - 98	90 - 98	100
NORTH INDIA	Mean	81	92	43	10	20	19	49	43	53	38	33	41	67	74	25	36	33	39	19	65	73	84	84	-
	range	61 - 96	83 - 98	36 - 57	2 - 18	14 - 25	19	49	32 - 61	53	25 - 61	33	34 - 54	53 - 77	55 - 89	24 - 26	19 - 53	16 - 55	26 - 51	8 - 25	57 - 76	73	74 - 90	68 - 92	-
WEST INDIA	Mean	93	95	53	20	29	31	33	87	85	61	23	85	80	98	-	61	38	23	56	88	85	91	94	99
	range	88 - 97	95	51 - 54	18 - 21	29	29 - 31	33	87	85	39 - 82	23	78 - 91	74 - 85	97 - 98	-	61	24 - 52	23	56	81 - 94	85	91	92 - 95	100
EAST INDIA	Mean	69	-	37	11	-	21		30	27	-	-	44	73	79	28	-	23	-	-	82	77	87	86	-
	range	69	-	37	11	-	21	-	30	27	-	-	44	73	79	28	-	23	-	-	40	77	87	86	-
NORTH EAST INDIA	Mean	97	93	59	45	-	-		75	-	59	-	-	90	97	-	-	48	-	83	93	-	-	-	-
	range	97	93	59	45	-	-	-	75		59	-	-	90	97	-	-	48	-	83	93	-	-	-	-
DELHI	Mean	84	96	41	16	-	-	-	40	29	86	-	36	71	86	21	34	27	-	23	80	72	83	86	50
	range	81 - 87	93 - 98	31 - 49	16	-	-	-	34 - 45	28 - 31	86	-	36	60 - 81	74 - 94	16 - 25	27 - 40	11 - 36	-	20 - 25	68 - 88	72	74 - 93	72 - 93	0 - 100

CENTRAL INDIA	Mean	88	83	36	-	-	13		19	-	-	-	21	61	78	-	6	3	-	18	32	36	66	64	-
	range	88	83	36	-	-	13	-	19	-	-	-	21	61	78	-	6	3	-	18	32	36	66	64	-