IJPSR (2021), Volume 12, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 August 2020; received in revised form, 06 September 2020; accepted, 23 May 2021; published 01 August 2021

PREVALENCE OF URINARY TRACT INFECTIONS AND RELATED ANTI-MICROBIAL RESISTANCE IN INDIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Keywords:

Anti-microbial resistance, Urinary tract infections, *E. coli*, Ampicillin, Meta-analysis

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ABSTRACT: Background: Urinary Tract Infections (UTIs) are one of the most commonly occurring infections in medical practice despite the widespread availability of antibiotics. This study aims to ascertain the prevalence of uropathogens and determine their antibiotic susceptibility or resistance patterns in the Indian population. **Methods:** A thorough search on the research studies concerning UTIs and their antibiotic susceptibility patterns in India was conducted through electronic databases including Google Scholar, Directory of Open Access Journals, Web of Science, Elsevier, *etc.* Search results were evaluated for the appropriateness of being included in the study. A total of 12 reports published from different regions of India were involved in the study. Analysis of data was performed using Comprehensive Meta-Analysis (CMA) software. **Results:** The most commonly isolated uropathogens were observed to be *E. coli*, and Klebsiella spp., with a prevalence of 49.6% and 12.8%, respectively. The highest mean resistance was found to be towards Ciprofloxacin, followed by Ampicillin. Resistance patterns in E.coli were found to be more towards Ampicillin (74.11%) and followed by Ciprofloxacin (61.32%). In the other uncommon uropathogens, the highest resistance was recorded towards Ampicillin (62.98%) and Ceftriaxone (62.7%). **Conclusions:** Over the past years, the resistance levels have been increasing gradually to the traditional drugs used for the treatment of UTI, and hence, a therapy based on the individual culture report and antibiotic sensitivity test is highly encouraged. The use of combinational drugs in the treatment of common infections may help reduce the spiking levels of resistance.

INTRODUCTION: Urinary Tract Infections (UTIs) are one of the most commonly occurring infections in medical practice despite the widespread availability of antibiotics [1]. Additional expenditures are incurred, costing billions of dollars worldwide, as these infections affect several people across the globe [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(8).4314-21

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(8).4314-21

UTIs occur in both men and women, but the incidence rate in women is higher when compared to men. Nearly half of the women population experience at least 1 episode of UTI in their lifetime, with 20-40% of them exhibiting recurrent episodes [3].

UTIs may involve the upper and the lower urinary tracts, with the lower UTIs being defined as cystitis and characterized by symptoms of dysuria, suprapubic tenderness, frequency, and urgency [4]. The most common pathogens causing UTIs include *Escherichia coli* and *Staphylococcus saprophyticus* followed by *Klebsiella pneumoniae* and *Proteus* spp [3].

Treatment is generally done with broad-spectrum antibiotics due to the concerns of antibiotic resistance. Fluoroquinolones were the most preferred initial agents as a part of the empirical therapy of the infections but are being limited due to high resistance rates and toxicity [5, 6].

Treatment may become challenging with the presence of risk factors like elderly age, immune-suppression, and other comorbidities. The extensive use of antibiotics over a period has stemmed from the development of antibiotic resistance, which has now become a problem worldwide. Since the etiology and antibiotic resistance of the uropathogens has not been constant over the years, the resistance patterns have not been studied extensively. Poor patient compliance leading to an incomplete course of antibiotic therapy has directed towards resistance to most of the antibiotics [7]. The selection of anti-microbial agents should not be decided by the most likely pathogen, but should rather be decided based on the susceptibility patterns. Hence, it is very important to know the patterns of local anti-microbial susceptibility to determine sensible and careful empirical therapy for the treatment of UTIs. To prescribe appropriate antibiotic therapy, the physician must have the required information about the cause of the infection as well as the susceptibility patterns. Therefore, it is important to determine the causative agents of UTI and their resistance patterns locally, in each region, so that a better and targeted therapy can be started before the culture and antibiotic sensitivity results, as these reports take long for processing [8, 9]. The current study is carried out by systematic review and meta-analysis of various studies in the field of bacterial drug resistance in UTIs to get more accurate and specific results.

A thorough exploration of research papers on the most common bacteria causing UTIs and their antibiotic resistance patterns in India was conducted through online electronic databases including Google Scholar, Scopus, PubMed, Embase, Directory of Open Access Journals (DOAJ), and Web of Science. Keywords involved were Urinary Tract Infections, Antibiotic Resistance, India, Gram-negative bacteria, and Gram-positive bacteria. The search results were evaluated, and their appropriateness and potentiality to be included in the study were determined. All the studies in the English language between the years 2000 to 2020 which reported the prevalence of uropathogens and their antibiotic resistance patterns among the Indian patients were studied systematically.

Inclusion and Exclusion Criteria: All cohort and cross-sectional studies that were associated with the antibiotic resistance patterns of various bacterial pathogens in UTIs were included. Studies that had derisory information, studies that were related to infections other than UTIs, review articles, congress and meeting abstracts, case reports, and research papers in languages other than English were excluded. To avoid bias, the search was carried out by two researchers independently.

Data Extraction: A special form was designed for researchers, which included data such as; the main author's name, year of publication, time and location of study, sample size, gender, average age, UTI causing bacterial pathogens, its prevalence, and resistance to various antibiotics.

Statistical Analysis: Analysis of data was performed using comprehensive meta-analysis (CMA) software. For the calculation of the event rate of UTI and anti-microbial resistance in each study, the sample numbers were determined and were used to calculate the variance.

Relative weights were allotted to each study. Calculations were reported by a 95% confidence interval. Due to the prevalence of heterogeneity in the studies, a random-effects model was used in the calculations.

RESULTS: Initially, a total of 93 articles were collected from different databases, which presented the relevant information. Based on the location and time of the study, about 36 of these articles were excluded based on the required criteria. Studies with inappropriate full text, review articles, and articles which emphasized only the susceptible patterns of uropathogens were excluded, resulting in 16 articles to be reviewed. Of these, 4 articles were found to be repetitive and were excluded. This resulted in the selection of 12 studies from different regions of the country to be analyzed.

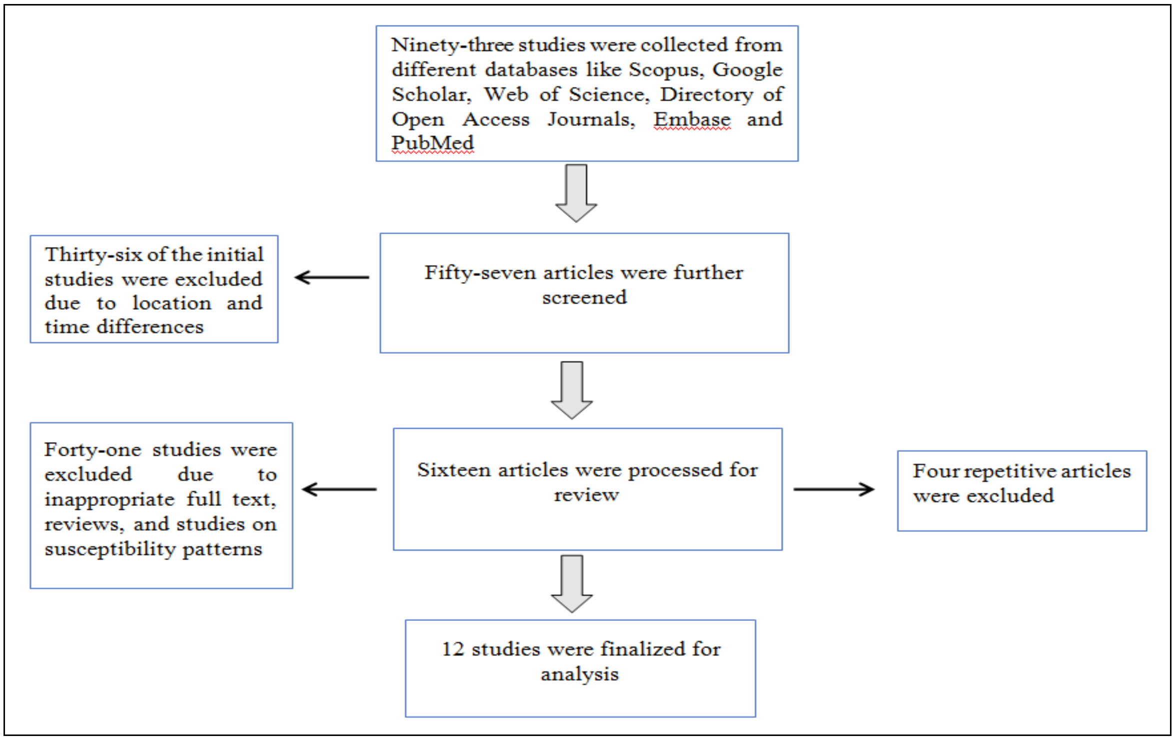

FIG. 1: FLOW-CHART DEPICTING THE PROCESS FOR THE SELECTION OF ARTICLES FOR META-ANALYSIS

More than half of the selected studies reported a higher affected population in women (about 43.31%) than men (30.69%). The most commonly isolated uropathogens were *E. coli*, and Klebsiella spp., with a prevalence of 49.6% and 12.8%, respectively. Other isolated organisms included *Proteus* spp., *Staphylococcus* spp., *Enterococcus* spp., *Pseudomonas* spp., *Enterobacter* spp., *Acinetobacter* spp., *Citrobacter* spp. along with species from Providencia, Morganella, Streptococcus, Aeromonas, and Serratia with a marginal frequency.

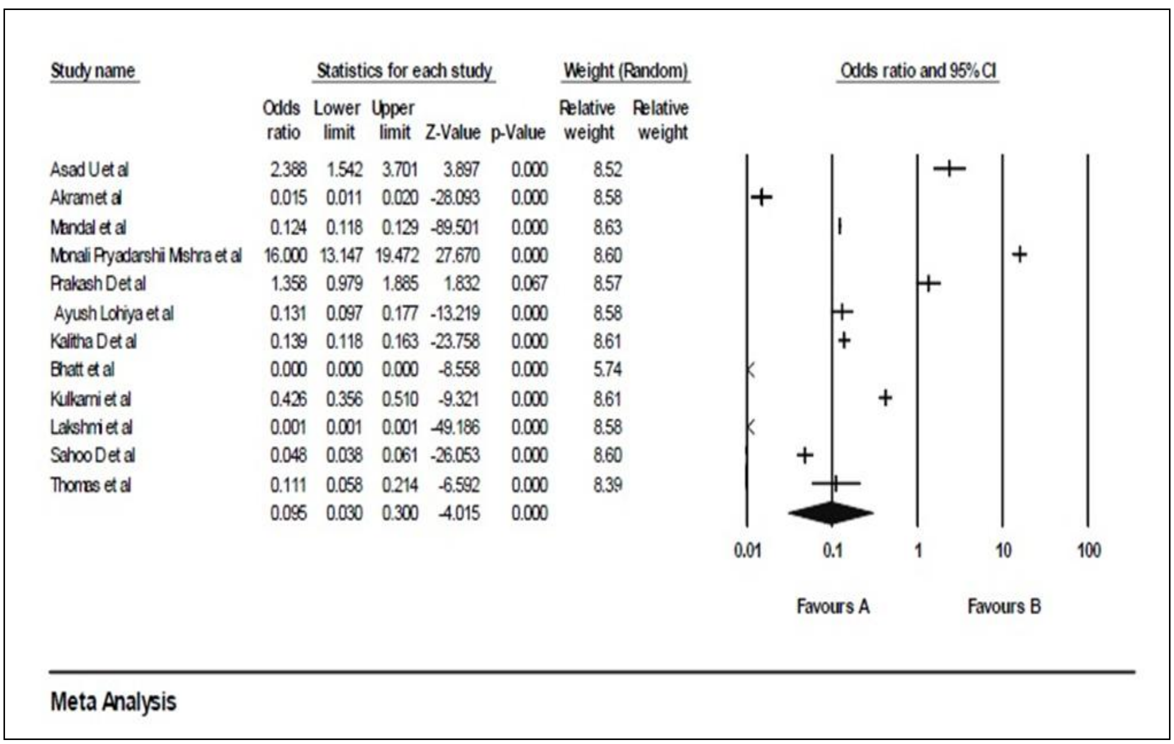

FIG. 2: FOREST PLOT ON THE META-ANALYSIS ON THE PREVALENCE OF UTI IN DIFFERENT STUDIES

The meta-analysis was performed on studies from different parts of India. General data from each study is represented in **Table 1**. All of the studies were published between 2006 and 2018 and included the aspects of the prevalence of UTIs in the population along with the resistance profiles of the uropathogens. A forest plot based on the odds ratio of prevalence of uropathogens **Fig. 2**, indicates greater chances for the occurrence of infections in patients.

TABLE 1: GENERAL DATA ACQUIRED FROM THE STUDIES IN THE META-ANALYSIS

S. no.	First author	Publishing year	Study year	Location of study	No. of samples	Prevalence of pathogens (in percent)
1	Asad U et al10	2006	2006	Aligarh	102	61%
2	Akram *et al* [11]	2007	2004-05	Aligarh	920	10.86%
3	Mandal *et al* [12]	2012	2008-09	Puducherry	19050	26.01%
4	MonaliPriya Darshini *et al* [13]	2013	2011-12	Odisha	1245	80%
5	D Prakash *et al*[14]	2013	2011-13	Meerut	288	53.82%
6	AyushLohiya *et al* [15]	2015	2012-13	Faridabad	433	26.5%
7	Kalitha et al[16]	2016	2013-14	Assam	1463	27.1%
8	Bhatt *et al*[17]	2017	2014-16	Pune	17135	15.9%
9	Kulkarni *et al*[18]	2017	2012-15	Bidar	1000	39.5%
10	Lakshmi *et al*[19]	2017	2017	Chennai	3408	30%
11	Sahoo*et al* [20]	2018	2014-16	Bhubaneshwar	1000	18%
12	Thomas *et al*[21]	2018	2015-16	Ooty	96	25%

TABLE 2: REPRESENTATION OF THE EVENT RATES OF VARIOUS ORGANISMS IN THE STUDIES

Organisms	No. of studies	Event rate	Z-value	P-value
E.coli	12	0.496	-0.861	0.389
Klebsiella spp.	9	0.128	-64.081	0.000
Proteus spp.	6	0.028	-56.820	0.000
Staphylococcus spp.	7	0.064		0.000
Pseudomonas spp.	8	0.063	-64.134	0.000
Acinetobacter spp.	4	0.065	-64.153	0.000
Enterobacter spp.	3	0.019	-61.700	0.000
Citrobacter spp.	5	0.020	-40.156	0.000
Enterococcus spp.	7	0.079	-44.465	0.000
Others	1	0.019	-64.276	0.000
Random		0.059	-38.045	0.000
			-5.808	

The organisms isolated in the selected studies, along with their event rates, are represented in **Table 2**. The event rate of *E. coli* was found to be the greatest, followed by *Klebsiella pneumoniae*. Other common organisms isolated in all studies were Proteus spp., Staphylococcus spp., Pseudomonas spp., Enterobacter spp., Acinetobacter spp., Enterococcus, and Citrobacter spp. Other organisms included Providencia, Morganella, Streptococcus, Aeromonas, and Serratia spp. Measurement of heterogeneity in the uropathogens isolated in each study produces an I2 value of 99.925, indicating considerable heterogeneity [22]. **Fig. 3** represents a funnel plot for the selected studies that exhibited asymmetry, indicating a publication bias either as delayed publication bias or a location bias [23].

TABLE 3: A META-ANALYSIS OF THE ISOLATED UROPATHOGENS IN THE STUDY

Model	Effect size and 95% CI				Heterogeneity		
Random	Number of uropathogens	Point estimate	Lower limit	Upper limit	Q-value	P-value	I^2
	10	0.061	0.025	0.141	11997.320	0.000	99.925

The overall resistance pattern of uropathogens is represented in **Table 4**. The highest mean resistance was found to be towards Ciprofloxacin, followed by Ampicillin. Resistance patterns in *E. coli*, the most common isolate, were found to be more towards Ampicillin (74.11%) and followed by Ciprofloxacin (61.32%). The resistance pattern of *E. coli* towards Ampicillin is represented in **Fig. 4**. Klebsiella spp. also reported the highest resistance towards Ampicillin (74.38%), followed by Gentamicin (56.88%).Proteus spp. reported an overall resistance of 80.04%, and 76.95% towards Ceftazidime and Ciprofloxacin, respectively. *Staphylococcus* spp. exhibited resistance towards Ampicillin (36.88%) and Cotrimoxazole (19.86%). Pseudomonas spp. exhibited the highest resistance towards Ceftazidime (60.18%) and Ciprofloxacin (50.72%). Acinetobacter spp. exhibited resistance towards Gentamicin (70.145) and Ceftazidime (59.78%). The highest resistance was exhibited towards Ceftriaxone (77.93%) and Ampicillin (74.02%) by *Enterobacter* spp. Gentamicin (46.83%) and Ampicillin (46.51%) were found to be most resistant to by Citrobacter spp. Enterococcus spp. exhibited greater resistance towards Ciprofloxacin (54.71%) and Tetracycline (52.53%). In the other uncommon uropathogens, the highest resistance was recorded towards Ampicillin (62.98%) and Ceftriaxone (62.7%).

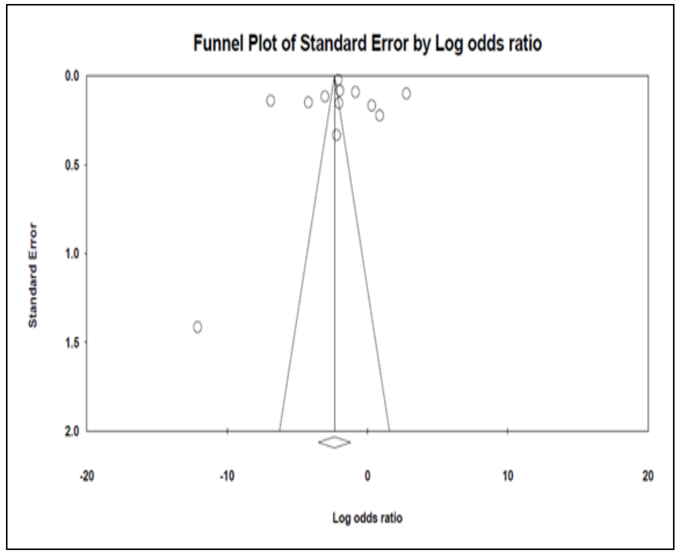

FIG. 3: FUNNEL PLOT TO REPRESENT PUBLICATION BIAS

TABLE 4: OVERALL RESISTANCE OF UROPATHOGENS TO COMMON ANTIBIOTICS

Antibiotics Uropathogens	AMK	CFP	CTZ	CEF	CIP	COT	GEN	PIP	NIT	NOR	ACL	AMP	CFR	NAL	CFX	MER
E. coli	21.47	30.08	55.94	3.67	61.32	25.21	48.57	23.4	23.17	9.79	30.86	74.11	11.13	2.21	34.66	4.8
Klebsiella spp.	25.82	33.60	62.1	1.77	56.44	24.91	56.88	29.44	49.63	10.07	27.61	74.38	7.95	1.3	32.45	10.93
Proteus spp.	27.54	56.38	80.04	1.95	76.95	30.95	58.95	50.1	24.03	6.83	48.93	47.84	3.62	2.99	3.25	25.26
Staphylococcus spp.	12.3	3.87	4.73	2.1	17.13	19.86	6.08	4.81	8.668	6.33	4.49	36.88	3.55	3.04	0	0.32
Pseudomonas spp.	24.38	37.04	60.18	2.78	50.72	12.34	48.06	32.06	9.76	9.4	8.3	7.95	8.93	1.65	1.39	27.5
Acinetobacter spp.	39.98	28.74	59.78	0.37	59.71	24.45	70.14	34.53	7.4	4.98	7.59	16.95	0	0	0.37	6.67
Enterobacter spp.	28.7	0	47.25	0.27	50.58	1.37	57.58	0	57.36	0	0	74.02	0	0.55	77.93	11.47
Citrobacter spp.	29.55	6.49	38.67	2.93	40.23	6.33	46.83	4.54	37.41	12.03	6.49	46.57	6.17	2.93	38.15	12.43
Enterococcus spp.	8.42	8.15	7.4	1.13	54.71	8.48	30.56	6.97	30.23	1.66	9.26	50.14	6.22	1.93	1.13	0
Others	47.01	0	49.37	0	57.93	0	53.34	0	61.58	0	0	62.98	0	0	62.7	26.25

AMK-Amikacin, CFP-Cefepime, CTZ-Ceftazidime, CEF-Cefotaxime, CIP-Ciprofloxacin, COT-Cotrimoxazole,GEN-Gentamicin, PIP-Piperacillin, NIT-Nitrofurantoin, NOR-Norfloxacin, ACL-Amoxyclav, AMP-Ampicillin, CFR-Cefuroxime, NAL-Nalidixic acid CFX-Ceftriaxone, MER-Meropenem

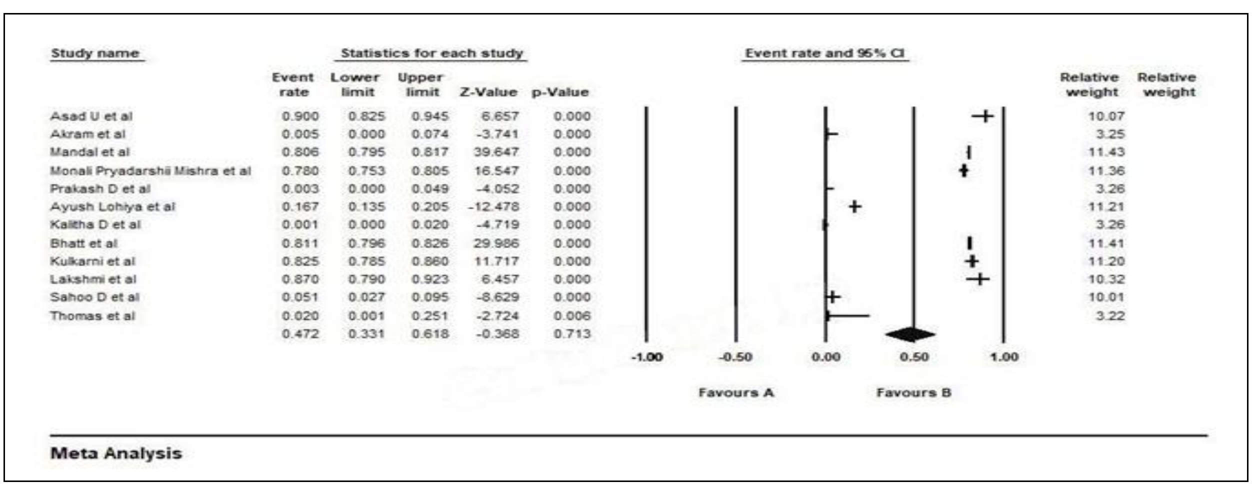

FIG. 4: FOREST PLOT REPRESENTING RESISTANCE PATTERNS OF *E. COLI* TOWARDS AMPICILLIN

DISCUSSION: The current study highlights the prevalence of UTIs to be more in women than in men. This comparison is similar to the results of other studies in regions like Gujarat [24], Patna [25], Rajasthan [3], and New Delhi [26]. The male urethra is13-20 cm long, whereas females possess a shorter urethra, approximately 3.8 to 5.1 cm long. This shortness of the urethra in women, along with proximity to the anal orifice, anatomically poses a greater risk of infection in women [27, 28]. There have been associations established between infections in the tract and sexual intercourse, use of spermicides, increasing age, menopause, and history of UTI [29, 30]. The most commonly isolated uropathogen was *E. coli*, bearing resemblance with the studies in Dehradun 6 by Biswas *et al.*, and in Haryana [31] by Arora G *et al.* Following E.coli were Klebsiella spp. in terms of prevalence, these results find similarity with the studies conducted in Nairobi [32], Iran [33], and Sri Lanka [34].

Drugs that were found to be the most resistant to various organisms were Ciprofloxacin and Ampicillin. A study conducted by Chooramani *et al*, in a tertiary care hospital in North India reported decreasing sensitivity patterns of uropathogens to Fluoroquinolones class of antibiotics [35]. A retrospective analysis of antibiotic resistance of uropathogens in South India performed by Somashekara SC et al revealed an 86% resistance to Ampicillin [36]. S Ny *et al.*, performed a study on the antibiotic resistance of *E. coli* in six European countries and Russia, the results yielded an overall high resistance to Ampicillin (39.6%) and Ciprofloxacin (15.1%) [37]. Klebsiella spp. have reported the highest resistance towards Ampicillin and Gentamicin, similar to the results of the study by Simon-Oke IA *et al.*, yielding a 53.6% and 34.4% resistance towards Ampicillin and Gentamicin respectively [38]. A study by Saha et al. on the susceptible patterns of antibiotics in West Bengal, indicates increased resistance of Klebsiella spp.to Penicillin combinations, Aminoglycosides, and third-generation Cephalosporins [39]. Proteus spp. was reported to exhibit resistance towards Ceftazidime and Ciprofloxacin. Taher I *et al.* reported a 68% and 64% resistance of Proteus spp. towards Ceftazidime and Ciprofloxacin respectively in Saudi Arabia [40]. Results on the antibiotic resistance patterns in Iraqi patients by Al-Naqshbandiet al; yielded significant resistance of Staphylococcus spp. towards Ampicillin and Ciprofloxacin, coinciding with the results of the current study [41]. Pseudomonas spp. exhibited a higher overall resistance in Ceftazidime and Ciprofloxacin, whereas Acinetobacter spp. expressed resistance towards Gentamicin and Ceftazidime. Analysis of the susceptibility rate of antibiotics in infected Chinese patients indicated decreased susceptibility of Acinetobacter spp. towards Ceftazidime [42]. A retrospective study conducted by DP Mohapatra *et al.* on extensively drug-resistant and pan-drug resistant bacteria in Eastern India revealed 59% of the isolated Acinetobacter spp. to be extensively drug-resistant and a total of 29.5% of Pseudomonas spp. to be extensively resistant [43]. A recent study by N. Omidifar *et al.* on antibiotic susceptibility patterns of uropathogens in pregnant women in Iraq reported resistance of 100% and 25% to Ampicillin and Ceftriaxone, respectively in Enterobacter spp., finding similarities in the current study [44]. A study by Goel *et al* in New Delhi revealed a high resistance of Tetracycline and Ciprofloxacin in seven different species of Enterococcus, bearing a resemblance to the results of the present study [45]. A retrospective study on antibiotic resistance of uropathogens in Karnataka, by Kalal BS *et al.*, revealed increasing levels of resistance, particularly in Gram-negative organisms like *E. coli*, *Klebsiella* spp., and *Proteus* spp. to antibiotics like Amoxicillin, Cephalosporins, and Fluoroquinolone antibiotics like Ciprofloxacin [46].

CONCLUSION: The increasing levels of antibiotic resistance in different regions of the country indicate alarming changes in the prescription patterns of antibiotics, a decrease in the OTC use of antibiotics for different conditions, and standardization in the manufacturing unit to avoid the distribution of spurious antibiotics. The prevalence of and resistance levels of *E. coli* was found to be very common among all the studies. This emphasizes a need for regular monitoring of the resistance levels of the organisms among the urban and rural populations. Over the past years, the resistance levels have constantly been increasing to the traditional drugs used for the treatment of UTI, and hence, a therapy based on the individual culture report and antibiotic sensitivity test is highly encouraged. Drugs like Ampicillin, Ciprofloxacin, Ceftazidime, Gentamicin, and

Ceftriaxone, commonly used to treat various infections, are most resistant to different organisms. The use of combinational drugs in the treatment of common infections may help reduce the spiking levels of resistance.

ACKNOWLEDGEMENT: We would like to express our gratitude to our beloved Principal Dr. V.Alagarsamy and Vice-Principal Dr. P. Subhash Chandra Bose for their constant encouragement and support.

CONFLICTS OF INTEREST: None declared

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How to cite this article:
Faraz MAA, Mendem S, Swamy MV and Patil S: Prevalence of urinary tract infections and related antimicrobial resistance in india: a systematic review and meta-analysis. Int J Pharm Sci & Res 2021; 12(8): 4314-21. doi: 10.13040/IJPSR.0975-8232.12(8).4314-21.