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Research Article

Antimicrobial Resistance Trends in Community Acquired Pneumonia at Secondary care Centres in Central India: Time to Develop Community Antimicrobial Stewardship Program

T Karuna[1], Ayush Gupta[2], Apurva Vyas[3], Shweta Kumar[4], Ananyan Sampath[5], Pramod Goel[6], Pankaj Shukla[7], Vivek Mishra[8], Sandeep Sharma[9], Sourabh Chakraborty[10], Shree Prakash Jaiswal[11], Abhi Mishra[12], Apoorwa Gupta[13], Manisa Sahu[14], Shreshtha Tiwari[15], Anisa Pal[16], Manish Nagendra[17], Harish Gautam[18], Kamlesh Patel[19], Shruti Asati[20], Mukul Nema[21], Sagar Khadanga[22]*

[1]Additional Professor, Department of Microbiology, AIIMS Bhopal, Madhya Pradesh, India

[2]Associate Professor, Department of Microbiology, AIIMS Bhopal, Madhya Pradesh, India

[3]Scientist C, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

[4]Research Associate III, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

[5]MBBS Student, AIIMS Bhopal, Madhya Pradesh, India

[6]Deputy Director, Quality Assurance, Govt. of Madhya Pradesh, India

[7]Ex. Director, National Health Mission, Govt. of Madhya Pradesh, India

[8]State Consultant, Quality Assurance, Govt. of Madhya Pradesh, India

[9]State Consultant, Quality Assurance, Govt. of Madhya Pradesh, India

[10]Consultant- Microbiology, Bansal Hospital, Bhopal, Madhya Pradesh, India

[11]Head of the Department, Pathology Department, Choithram Hospital, Indore, Madhya Pradesh, India

[12]Microbiologist, Govt. P C Sethi Hospital, Indore, Madhya Pradesh, India

[13]Microbiologist, Rajshree Apollo Hospital, Indore, Madhya Pradesh, India

[14]Senior Consultant- Microbiology, Balco Medical centre, Raipur, Chhattisgarh, India

[15]Consultant-MicrobiologyICO, Balco Medical centre, Raipur, Chhattisgarh, India

[16]Microbiologist, Jabalpur Hospital and Research Centre, Jabalpur, Madhya Pradesh, India

[17]Associate Professor, Netaji Subhash Chandra Bose Medical college, Jabalpur, Madhya Pradesh, India

[18]Microbiologist, Govt. Jai Prakash Hospital, Bhopal, Madhya Pradesh, India

[19]Microbiologist, Medanta Hospital, Indore, Madhya Pradesh, India

[20]Assistant Professor, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

[21]CEO and Quality Head, Anant Nursing Home PVT. LTD. Jabalpur, Madhya Pradesh, India

[22]Associate Professor, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

***Corresponding author:** Dr. Sagar Khadanga, Associate Professor, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India.

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Abstract

Background: Community acquired pneumonia (CAP) is a significant global health burden, with high morbidity and mortality especially in developing nations. This study assessed the changing pattern of anti microbial resistance (AMR) in CAP in secondary care centres of central India. **Methodology:** This was a prospective observational study conducted in 10 secondary care centres in smaller cities of Central India in the state of Madhya Pradesh. **Result:** Among the 1315 respiratory samples analysed, 49.5% (651/1315 samples) showed significant pathological growth out of which 47.6% (626 /1315) showed bacterial growth and 1.9% (25/1315) showed fungal growth. Gram-negative bacteria accounted for 94.2% (590/626 samples) and Gram-positive bacteria for 5.7% (36/626 samples). *Klebsiella pneumoniae* was the most prevalent Gram-negative isolate (45%), followed by *Pseudomonas aeruginosa* (24.2%) and *Acinetobacter spp* (15.42%). Third generation cephalosporin resistance was observed in 84.6% in *E. coli* and 81.1% in *K. pneumoniae*. Carbapenem resistance was highest in *Acinetobacter* spp (79.1%) followed by *E. Coli* (45.6%), *K. pneumoniae* (37.2%) and *P. aeruginosa* (35.7%). Colistin resistance was observed in less than 10% of all gram negative isolates with the highest being in *P. aeruginosa* (9.8%), *K. pneumoniae* (7.9%), *Acinetobacter spp* (6.6%) and *E. Coli* (2.9%). Among the gram-positive isolates, 51.7% of *Staphylococcus aureus* were MRSA and 9.70% were resistance to vancomycin. **Conclusion:** AMR is no more restricted to tertiary care centres in bigger cities of India. The menace of AMR is too critical to be ignored in primary and secondary care settings. This study highlights the importance of adopting a community level 'One-Health' multidisciplinary approach in human-animal health and soil-environment.

Keywords: Respiratory tract infections; Drug resistance; Microbial; Antimicrobial stewardship; Enterobacteriaceae; Gram positive bacteria; Pneumonia

Introduction

Respiratory tract infections (RTI) represent the highest burden of infectious diseases in the world, accounting for a substantial proportion of morbidity and mortality especially in developing nations [1-4]. RTI contribute to over 500 million cases and about 50 million annual deaths accounting to 13.4% of all disability adjusted life years across the globe [5-8]. The incidence of RTI and associated mortality/morbidity vary on several factors such as age, geographical location, seasons, local antimicrobial prescription practices and the prevailing antimicrobial resistance (AMR) patterns [9-14].

RTI affecting the upper and lower respiratory tract are caused by a diverse group of pathogens, including bacteria, viruses, fungi, and parasites [15,16]. The scary six bacteria (*Klebsiella pneumoniae, Escherichia coli*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus)* are responsible for the majority of deaths in pneumonia. Majority of these organisms are multi drug resistant or extensively drug-resistant. RTIs are the most common cause of antibiotic abuse leading to anti microbial resistance (AMR) and also contribute to majority of deaths caused by multi drug resistant organisms [4,17].

India, as a developing nation, having the world's largest population and not so well regulated antibiotic practices is uniquely placed in the global AMR campaign [18]. Indian Council of Medical Research (ICMR) has initiated nationwide "Antimicrobial Resistance Surveillance and Research Network" (AMRSN) [19,20]. After successfully consolidating anti-microbial stewardship program (AMSP) at various tertiary care centres, AMRSN has envisaged extending to secondary care centres across India as a hub-spoke model. The state of Madhya Pradesh in India has developed state action plan for containment of antimicrobial resistance (MPSAPCAR) in 2019 on the guidelines of National Action Plan on AMR (NAP AMR).

The present study was conceived to identify the pattern of antibiogram for RTIs in secondary care hospitals (district hospitals / nursing homes) at central India with support from ICMR-AMRSN and MPSAPCAR.

Methodology

Study Setting and Ethical Clearance: This prospective longitudinal observational chart review study was conducted in the state of undivided Madhya Pradesh in central India. Among the nominated 10 secondary care centres, two hospitals were government district level hospitals and the remaining eight study-sites were private nursing homes, located in urban/semi-urban areas. These sites were chosen based on the availability of in-house accredited microbiology laboratory and a full-time microbiologist. The location of these cities is presented in Figure 1.

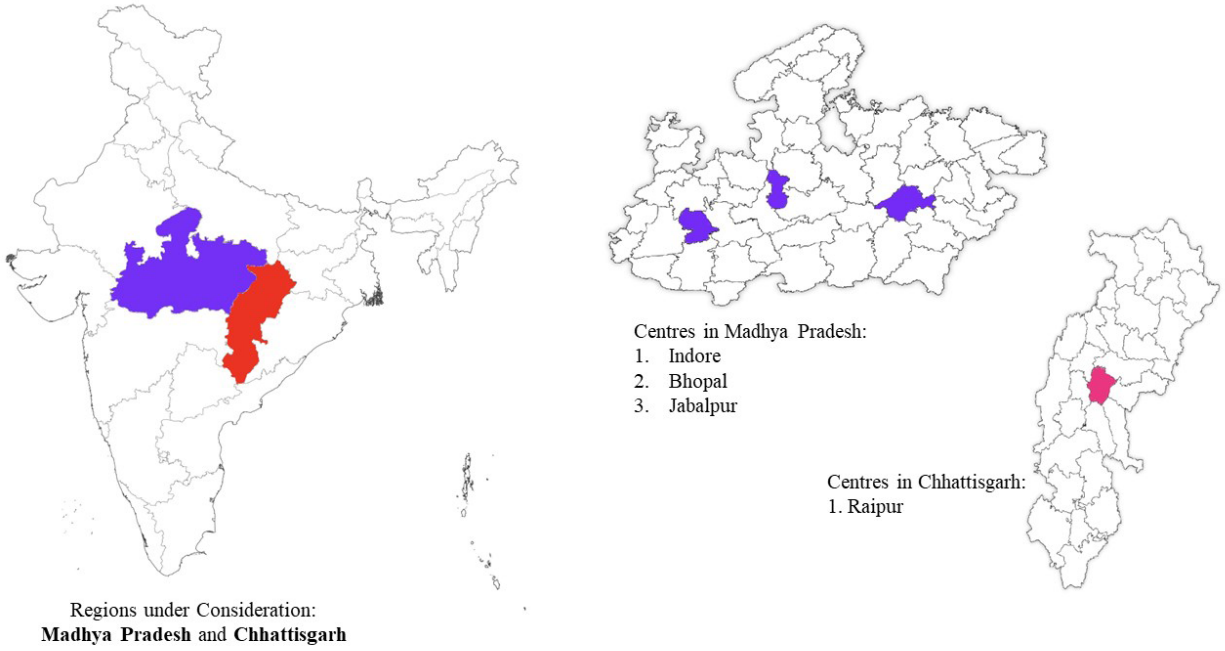


Figure 1: AIIMS Bhopal ICMR-AMRSN initiated network.

The study was carried out as part of ICMR-AMRSN, with Institute Human Ethics Committee (IHEC) approval Letter No. LOP/2020/EF0157 dated February 24, 2020. As the study was only observational and chart review without any patient identifier, hence waiver of consent was granted by IHEC. The present data set was collected from 1st April 2022 to 30 September 2022. The study procedure was in accordance with the principles of the Declaration of Helsinki. Training protocols provided by ICMR-AMRSN were customised at All India Institute of Medical Sciences, Bhopal, for these secondary care centres.

Sample size and sampling: Formal sample size was not calculated. Consecutive and feasible sampling was adopted. Antibiograms were generated only for those organisms with a cumulative frequency of more than 30 samples.

Sample Collection: Sputum (spontaneous or induced) samples and endo-tracheal (ET) tube aspirates from symptomatic patients (fever and/or cough and/or clinical chest sign and infiltration in X-ray) were sent for aerobic culture as per CLSI guidelines. Routine nasopharyngeal swabs and routine endo-tracheal tube aspirates from asymptomatic patients were not taken into consideration. The collected specimens were promptly transported to the laboratory as soon as possible (preferably within 1 hour).

Microbiological isolation and reporting: Clinical data were collected by the nursing officers, and the microbiological data were collected by the laboratory technician and verified by the microbiologist. Prior to processing for culture, the sputum specimens were checked for appropriateness of collection by Murray & Washington criteria. Appropriate sputum samples were cultured on Chocolate agar, Sheep blood agar and MacConkey agar and incubated at 35±2ºC under aerobic conditions with 5-10% CO_2 for overnight incubation. Plates were examined each day for up to 72 hours for colonies of interest. The identification of colonies of interest was based on their cultural and morphological characteristics followed by conventional biochemical tests and susceptibility testing by Kirby-Bauer disk-diffusion method. Results of antimicrobial susceptibility were interpreted as per CLSI-M100.

Antimicrobial Resistance Patterns: Third-generation cephalosporin susceptibility for the Enterobacteriaceae family was reported when susceptible to ceftriaxone and for *Pseudomonas* using ceftazidime. 3rd generation cephalosporin resistance (3rd GCR) was calculated by 100 minus the susceptibility percentage of ceftriaxone/ceftazidime. Carbapenem resistance was calculated by 100 minus the susceptibility percentage of meropenem. Methicillin resistance was calculated by 100 minus the susceptibility percentage of oxacillin.

Data Analysis: Cleaned data were entered in a spreadsheet, and the data were summarized as frequencies and percentage up to one decimal value.

Result

Out of the 1315 respiratory samples, 651 (49.5%) showed significant pathological growth. Among the positive cultures (n=651), 626 (96.1%) showed bacterial growth, and 25 (3.8%) were *Candida spp*. Among the bacterial growth (n=626), 590 (94.2%) were Gram-negative bacteria, and 36 (5.7%) were Gram-positive bacteria.

Among the Gram-negative isolates (n=590), the predominant isolate was *Klebsiella pneumoniae* (266, 45%) followed by *Pseudomonas aeruginosa* (143, 24.2%) and *Acinetobacter spp* (91, 15.4%). The prevalence of other isolates is given in detail in Table-1. The susceptibility patterns of the identified pathogens to different antibiotics were analysed and provided below.

Table 1: Spectrum of culture positive isolates.

Total culture positive Isolates	49.5% (651/1315)
Total bacterial isolates	96.1% (626/651)
Gram negative bacterial isolates	90.6% (590/651)
Klebsiella pneumoniae	40.8% (266/651)
Pseudomonas aeruginosa	21.9% (143/651)
Acinetobacter spp.	13.9% (91/651)
Escherichia coli.	10.4% (68/651)
Enterobacter spp.	3.3% (22/651)
Gram positive bacterial isolates	5.5% (36/651)
Staphylococcus aureus	4.9% (32/651)
Enterococcus spp.	0.6% (4/651)
Others (Candida spp.)	3.8% (25/651)

***Klebsiella pneumoniae*:** Resistance to 3rd generation cephalosporin was noticed in 81.1% cases, piperacillin resistance was in 56.6% cases, carbapenem resistance in 37.2% and colistin resistance in 7.9%. The detailed antibiogram of *Klebsiella pneumoniae* is provided in Figure-2A.

***Escherichia coli*:** Resistance to 3rd generation cephalosporin was noticed in 84.6% cases, piperacillin resistance in 61.3% cases, carbapenem resistance in 45.6 % and colistin resistance in 2.9 % of cases. The detailed antibiogram of *Escherichia coli* is provided in Figure- 2C.

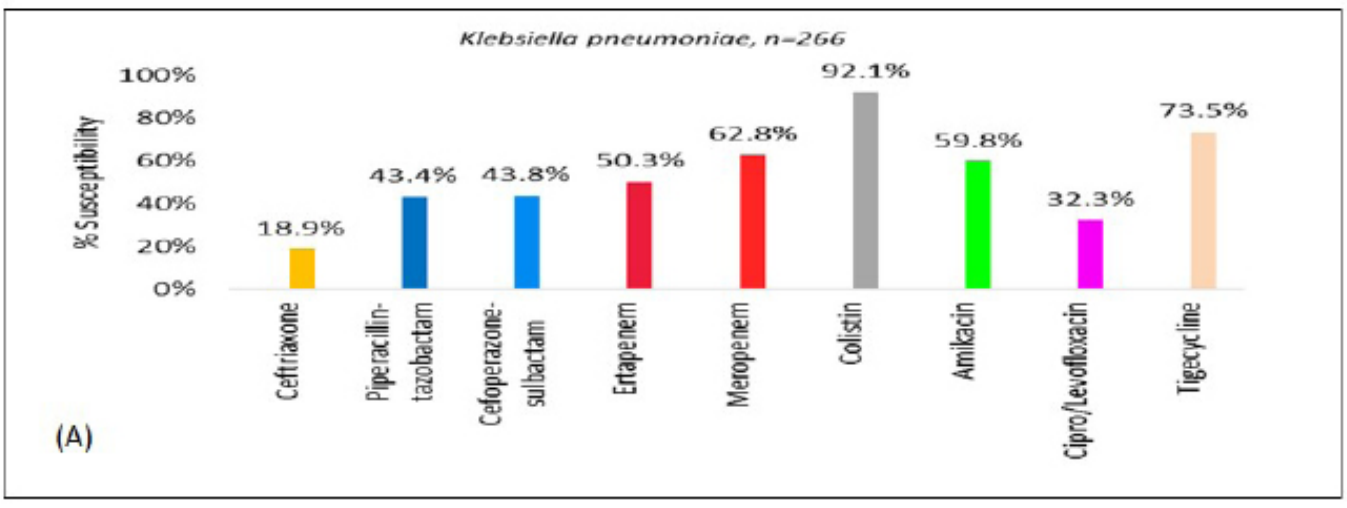
***Acinetobacter spp*:** Resistance to piperacillin was noticed in 83.5% cases, carbapenem resistance in 79.1% and colistin resistance in 6.6% of cases. The detailed antibiogram of *Acinetobacter* spp isolates is provided in Figure-2B.

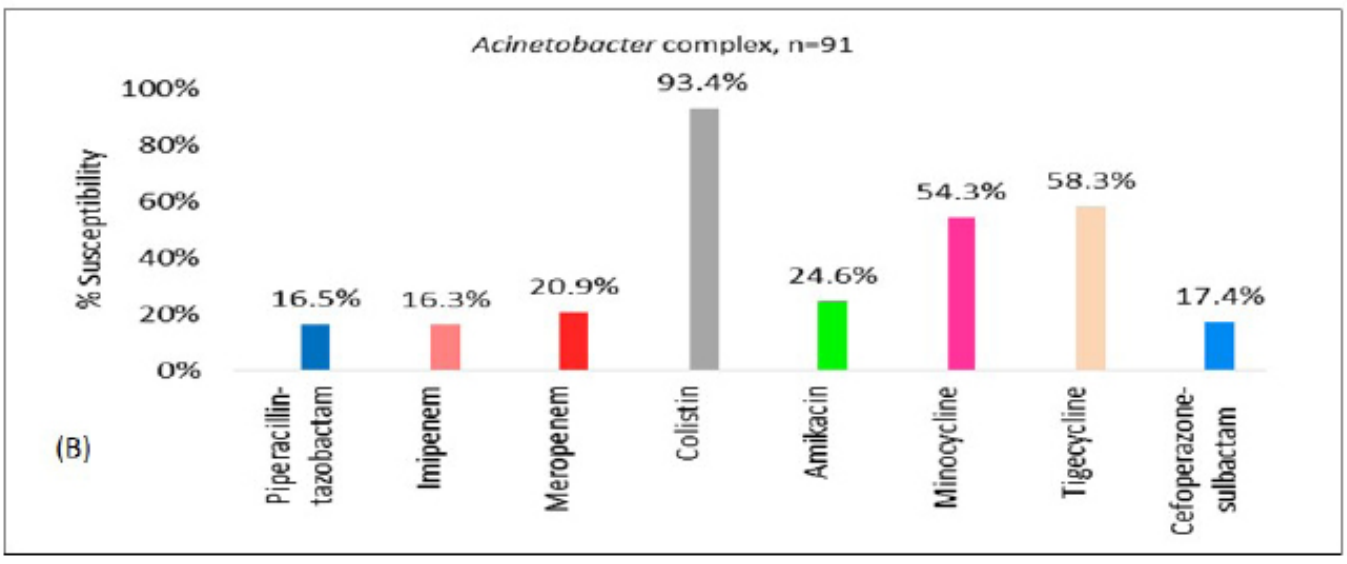
***Pseudomonas aeruginosa*:** Resistance to 3rd generation cephalosporins was observed in 46.6% of cases, piperacillin resistance in 38.2% cases, carbapenem resistance in 35.7% and colistin resistance in 9.8% of cases. The detailed antibiogram of *Pseudomonas aeruginosa* is provided in Figure-2(D).

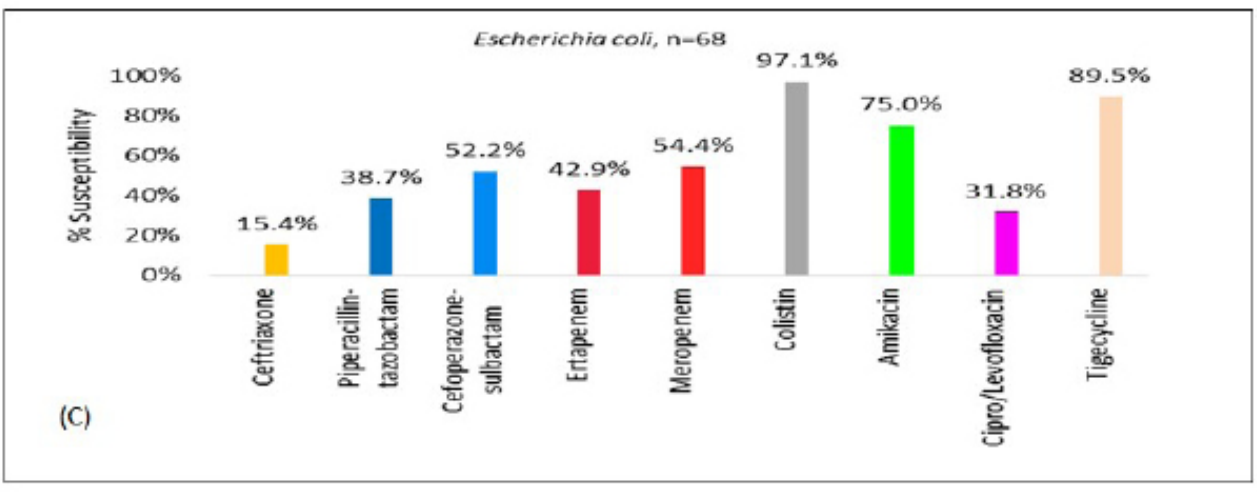
Staphylococcus aureus: Vancomycin resistance was seen in 9.7% of cases and linezolid resistance in 16.7% of cases. The detailed antibiogram of *Staphylococcus aureus* isolates is provided in Figure-2(E).

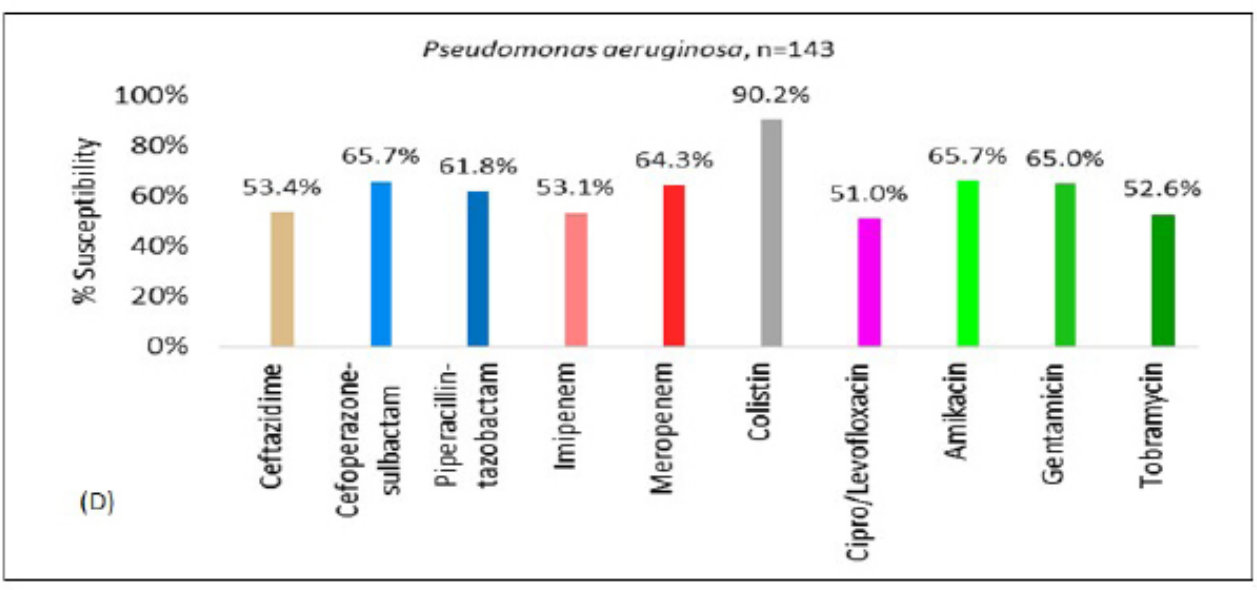
Discussion

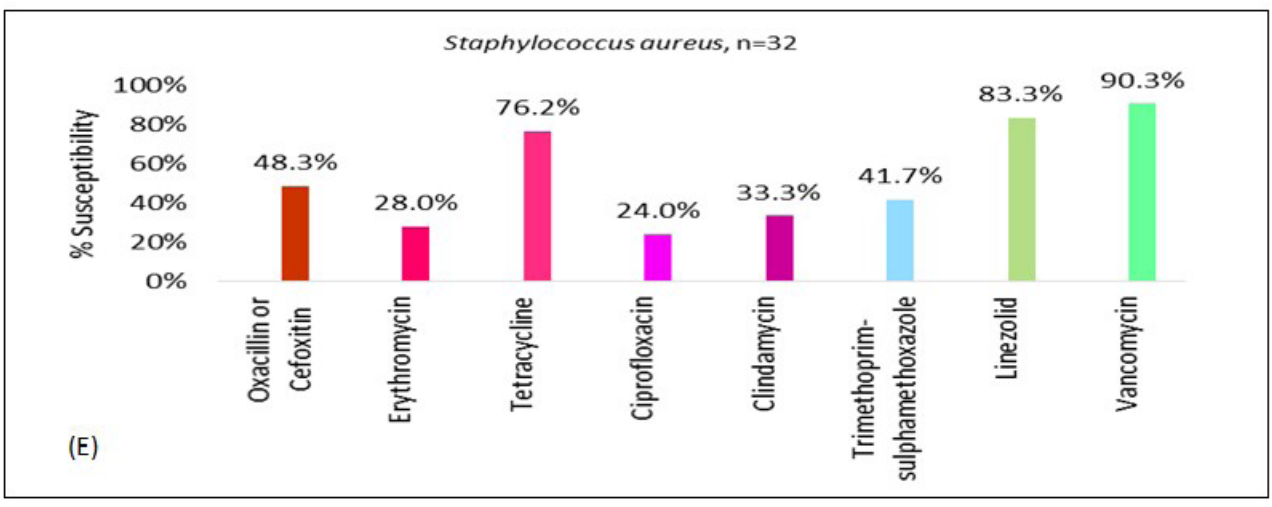
Approximately 1.2 million individuals succumb to AMR annually, and an estimated 10 million more may face the same fate by the year 2050 [4,21]. According to economic predictions, the global economy may experience a decline of 2-3.5% in gross domestic product (GDP) by 2050, and a drop of 3-8% in livestock as a result of AMR, with the potential cost of USD 100 trillion [17]. Even after an extensive literature review, we found scanty literature that analysed the prevalence of AMR among primary and secondary care centres of respiratory pathogens in India. Most of these studies focus mainly in intensive care units of tertiary care centres. A comparative analysis of observed global AMR patterns in non-tertiary care centres is presented below in Table-2. This study serves as a projection as to how far the menace of AMR has percolated down.











(A) *Klebsiella pneumoniae* **(B)** *Acinetobacter complex* **(C)** *Escherichia coli* **(D)** *Pseudomonas aeruginosa* **(E)** *Staphylococcus aureus*

Figure 2: Susceptibility pattern of Gram-Negative Bacilli (GNB) and Gram-Positive Cocci (GPC) in secondary care hospitals.

Table 2: Comparative Antimicrobial Resistance Patterns of Organisms to Specific Antimicrobial Agents.

Organism	Category	Present Study	Rajasthan, India [16]	Turkey [22]	North America [23,24]	Europe [23,24]	Asia pacific region [23,24]	Latin America [23,24]
Escherichia coli	3rd generation cephalosporin resistant (Ceftriaxone)	84.6%	72.8%	62.0%	25.6%	24.7%	24.3%	45.5%
	Carbapenem resistant (Meropenem)	45.6%	10.3%	3.5%	0.7%	0.5%	1.0%	0.0%
	Colistin resistant	2.9%	NA	1.7%	0.1%	1.1%	0.0%	0.0%

Klebsiella pneumoniae	3rdgeneration cephalosporin resistant (Ceftriaxone)	81.1%	63.9%	72.6%	18.4%	41.4%	25.1%	42.9%
	Carbapenem resistant (Meropenem)	37.2%	21.3%	45.1%	6.5%	14.2%	6.1%	17.9%
	Colistin resistant	7.9%	NA	18.5%	1.9%	7.2%	2.2%	8.1%
Pseudomonas aeruginosa	3rdgeneration cephalosporin resistant (Ceftazidime)	46.6%	9.7%	31.5%	17.8%	27.6%	15.8%	14.1%
	Carbapenem resistant (Meropenem)	35.7%	8.0%	34.3%	22.7%	33.7%	19.7%	24.8%
	Colistin resistant	9.8%	NA	7.5%	0.4%	0.2%	0.3%	0.0%
Acinetobacter	Carbapenem resistant (Meropenem)	79.1%	33.1%	93.1%	43.8%	83.0%	78.8%	85.0%
	Colistin resistant	6.6%	NA	12.8%	9.5%	16.3%	10.6%	3.3%
Staphylococcus aureus	MRSA	51.7%	56.9%	NA	44.0%	26.4%	39.4%	34.8%
	Vancomycin resistant	9.7%	NA	0.0%	0.0%	0.0%	0.0%	0.0%
NA – Not Available								

A similar extensive study has been reported in SENTRY trial from Latin America analysing patterns of AMR in different infections highlighting the need for community level anti microbial stewardship practices [24,25].

Gram negative isolates predominated in our study, similar to reports by Singh et al. (2020, India), Sarmah N et al (2016, India), Gebre, A. B et al. (2021, Ethiopia), and Duan D et al (2020, China) [15,16,26,27]. In contrast to our study, *Streptococcus pneumonie*, *Haemophilus influenzae* and *Moraxella catarrhalis* have been found to be the predominant organisms in some other studies [28,29].

Klebsiella pneumoniae was the single most common isolated organism in our study, similar to Singh et al (2020, India) and Sarmah N et al (2016, India). Similar to our study Singh et al (2020, India) also documented higher incidence of 3rd generation cephalosporin resistance (63.9% in *Klebsiella pneumoniae* and 72.8% in *Escherichia coli)* and carbapenem resistance (21.3% in *Klebsiella pneumonia* and 10.3% in *Escherichia coli)*. Colistin resistance in *Klebsiella pneumoniae* (7.9%) and *Escherichia coli* (2.9%) was not observed so frequently in our study. However, Gandra et al, (2017, United Kingdom) reported high fatalities (70%) associated with colistin-resistant *K. pneumoniae* and over 70% of the isolates were resistant to fluoroquinolones and third generation cephalosporins [16,26,30].

In our study, *Acinetobacter* species showed 79.1% of carbapenem resistance similar to the study by Sahu et al. (2006, India), Gonlugur, U et al. (2004, Turkey) [31,32]. Studies by Struelens MJ et al. (1993, Canada), and M.Todd Lewiset al. (1999,Korea), susceptibility to imipenem was found to be over 95%, whereas in studies conducted in Turkey, the susceptibility was reported to be 55.5% by Forster DH et al. and 80.5% by Gonlugur, U et al.

The SENTRY trial conducted in Brazil and Latin America in 2008 was indicative of high resistance rates among beta lactams and cephalosporins among the isolated *Pseudomonas aeruginosa* samples, attributed to the genetic potential of the organism as well as improper administration of antibiotics in the region [25]. In contrast to these results, the ICMR AMR report (India, 2021) observed a comparatively lower resistance of *Pseudomonas* to beta-lactams and aminoglycosides, with rates very similar to our study [33]. Other studies conducted by Ibrahim ME. Et al (2018, Saudi Arabia), Ahmed SMA et. al (2018, Sudan) shows very high resistance to aminoglycosides but a higher resistance rate to beta-lactams, aminoglycosides and fluroquinolones [34,35].

Limitations

Our study has several limitations. A formal sample size was not calculated and feasible sampling strategy was adopted. Organisms with a cumulative frequency of more than 30 samples were included in the analysis and development of antibiogram. The microbiological data was collected from relatively smaller nursing homes and district hospitals with potentially lower levels of quality control. The detailed demographic, clinical and final outcome data were not available, precluding stratified data analysis. Speciation of *Acinetobacter spp*. and *Enterococcus spp*. isolates could not be performed due to logistic issues.

Conclusion

Antimicrobial resistance (AMR) is no more restricted to bigger cities in India. The menace of AMR has percolated into primary and secondary care centres of India in smaller cities implying more multi drug resistance cases in community acquired

infections especially in respiratory tract infection. In presence of not so organised health care sectors in smaller cities of India, AMR related morbidity and mortality will be a huge challenge in years to come. As of now, there are no separate focused strategies for community AMR campaign by global action plan on AMR (GAP AMR) and Indian national action plan on AMR (NAP AMR). Time is imperative to devise community level anti microbial stewardship practices with one health approach involving human-animal health and soil-environment.

Declarations

Conflicts of Interest: There are no conflicts of inserts among the authors. The corresponding author SK received grants from ICMR to conduct the study.

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Institutional Review Board Statement: This project was granted clearance by the institutional ethics committee of AIIMS Bhopal vide LOP/2020/EF0157 dated February 24, 2020.

Informed Consent Statement: This study was designed and carried out as per the guidelines of Helsinki, Good clinical practice guidelines and followed the ICMR ethics handbook at all stages of planning, data acquisition, analysis and dissemination. All participants were recruited after informed written consent as per ICMR guidelines.

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Author's contribution details:

	Concept	Design	Data acquisition	Data Analysis	Manuscript preparation	Manuscript editing	Manuscript review
TK	✓	✓	✓	✓	✓	✓	✓
AYG	-	✓	✓	✓	✓	✓	✓
AV	-	-	✓	✓	✓	✓	✓
SK	-	-	✓	✓	✓	✓	✓
AS	-	-	-	✓	✓	✓	✓
PG	-	-	✓	✓	✓	✓	✓
PS	-	-	✓	✓	✓	✓	✓
VM	-	-	✓	✓	✓	✓	✓
SS	-	-	✓	✓	✓	✓	✓
SC	-	-	✓	-	✓	✓	✓
SPJ	-	-	✓	-	✓	✓	✓
AM	-	-	✓	-	✓	✓	✓
AG	-	-	✓	-	✓	✓	✓
MS	-	-	✓	-	✓	✓	✓
ST	-	-	✓	-	✓	✓	✓
AP	-	-	✓	-	✓	✓	✓
MN	-	-	✓	-	✓	✓	✓
HG	-	-	✓	-	✓	✓	✓

KP	-	-	✓	-	✓	✓	✓
SA	-	-	✓	-	✓	✓	✓
MN	-	-	✓	-	-	✓	✓
SKH	✓	✓	✓	✓	✓	✓	✓

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