

# Antimicrobial resistance (AMR) at the community level: An urban and rural case study from Karnataka

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## ABSTRACT

**Context:** The emergence of antimicrobial resistance (AMR) is a major public health crisis in India and globally. While national guidelines exist, the sources of data which form the basis of these guidelines are limited to a few well-established tertiary care centres. There is inadequate literature on AMR and antibiotic mismatch from India at community level and even less literature on AMR patterns from rural India. **Aims:** The aims of this study were as follows: 1) to describe the patterns of AMR at an urban tertiary care hospital and a rural 100 bedded hospital; 2) to compare and contrast the AMR patterns noted with published ICMR guidelines; 3) to examine the issue of AMR and antibiotic mismatch; and 4) to identify local factors influencing drug-bug mismatch at the local level. **Settings and Design:** The data were obtained from two independently conceived projects (Site 1: Urban tertiary care hospital, Site 2: Rural 100-bedded hospital). **Methods and Materials:** Local antibiograms were made, and the antibiotic resistance patterns were compared between the urban and rural sites and with data published in the 2017 ICMR national guideline for AMR. **Statistical Analysis Used:** Descriptive statistics including means and medians were used. **Results:** Our data reveal: a) a significant mismatch between sensitivity patterns and antibiotics prescribed; b) The national guidelines fail to capture the local picture of AMR, highlighting the need for local data; and c) challenges with data collection/retrieval, access and accuracy of diagnostic tools, administrative issues, and lack of local expertise limit antimicrobial stewardship efforts. **Conclusions:** Our study finds the burden of AMR high in both rural and urban sites, reinforcing that AMR burden cannot be ignored in rural settings. It also highlights that national data obtained from tertiary care settings fail to capture the local picture, highlighting the need for local data. Mechanisms of linking rural practices, primary health centres, and small hospitals with a common microbiology laboratory and shared data platforms will facilitate antibiotic stewardship at the community level.

**Keywords:** Antibiogram, antibiotic policy, antimicrobial stewardship, community level AMR, rural health

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## Introduction

Worldwide, due to antimicrobial resistance (AMR) and resulting inadequate treatment of bacterial infections, 700,000 lives are lost per year and is predicted to increase to around 10 million people

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every year by 2050 costing the global economy about 100 trillion USD that includes loss of productivity.<sup>[1]</sup>

Understandably, AMR is a major public health crisis in India too.<sup>[2]</sup> As reported in 2015, the burden is estimated to be around 2 million deaths by 2050.<sup>[3]</sup>

Key factors driving AMR in India are: a) unregulated access to antibiotics (with or without prescriptions); b) financial incentives to prescribe antibiotics; and c) patient demand.<sup>[4]</sup> Additionally, antibiotic use is rampant in the food, livestock, agriculture, and environment sectors which in turn increase the cumulative AMR burden in the country.<sup>[5,6]</sup> In an observational study among 71 countries, it was noticed that there was a 36% raise in overall consumption of antimicrobials between 2000 to 2010 (India, Brazil, China, Russia and South Africa accounted for 76% of consumption)<sup>[7]</sup>

An antibiogram is a practice and educational tool that aids clinicians with empirical treatment for common infections within their local practice context, enables continuous surveillance, and facilitates practice modification in an iterative manner over time. It informs everyday practice by advising clinicians specifically on the preferred antibiotic to use by clinical syndrome. It also identifies antibiotics to avoid or use within a restricted procedural framework. Hence, having this tool and antibiotic guidelines in public primary health care centres as well as private practices that are locally relevant ensures optimal treatment and reduces the cost of antibiotic mismatch or over prescription. However, generating and updating local antibiograms come with its challenges even with advanced scientific tests and technology in health.

As a part of the National Action Plan – AMR, the Indian Council of Medical Research (ICMR) has established a National Programme on Antimicrobial Surveillance (Antimicrobial resistance surveillance and research network).<sup>[8]</sup> This program focuses on clinically relevant pathogens identified by the World Health Organization-based primarily at tertiary care academic centres. A notable gap is the paucity of published data from community practice settings that capture local AMR trends. Such data are essential to inform local antimicrobial stewardship efforts.

In this paper, we use two case studies, one from an urban tertiary care hospital and another from a rural 100-bedded hospital to highlight the patterns of AMR at the community level. We also illustrate the critical role of multidisciplinary teamwork in the collection, analysis, representation, and translation of data pertinent to AMR into clinical practice. Our specific aims were to: 1) describe the patterns of AMR at an urban tertiary care hospital and a rural 100 bedded hospital; 2) compare and contrast the AMR patterns noted between the two sites and the published ICMR guidelines; 3) examine the issue of AMR and antibiotic mismatch; and 4) identify local factors influencing drug-bug mismatch at the facility level.

The study emphasises the importance of having mechanisms to have local antibiotic resistance patterns at community level in primary care practices for antibiotic stewardship, and we have

also tried to discuss the various challenges involved in the same and possible measures to overcome them.

## Materials and Methods

The data were obtained from two independently conceived projects, whose methods are described below.

### Urban site – Tertiary care hospital, Bengaluru

This was a hospital-based prospective observational audit that was conducted from May to November 2017. This was cleared by the local institutional ethics board in the urban setting and the clearance was obtained in May 2017. The PharmD resident (author: PS) collected data related to antimicrobial susceptibility and antibiotic use patterns (including escalation and de-escalation) from patient case sheets and interviews with patients or bystanders. Inclusion Criteria: All inpatients (IPs) who received antimicrobials in the medical and surgical wards of a tertiary care hospital, Bengaluru. Exclusion criteria: Pregnant and lactating women and patients who were not willing to participate in study. The intent of this audit was twofold: a) to identify antibiotic resistance patterns and b) to compare the AMR pattern found with the empirical antibiotics prescribed. The mismatch between the empirical antibiotics prescribed and the culture reports were captured by the patterns of escalation and de-escalation. For the purpose of this paper, we have included non-ICU patients from the overall data collection.

### Rural site – 100 bedded secondary care hospital Saragur, Mysore

This was a hospital-based retrospective chart audit to create an antibiogram for antibiotic stewardship in the hospital. The study was conducted in two phases. Phase-1 from July 2016 to May 2017 and Phase-2 from May 2017 to November 2018. This was done as a quality improvement project, and since this was conducted for the purpose of antibiotic stewardship, it was not submitted to the Institutional Ethics Committee for approval but formal permission and support through written documentation from the hospital administrative department was received. The data were collected from the patient registry maintained at the in-house laboratory and the external laboratory website. Inclusion Criteria: All bacterial cultures isolated from urine, pus, sputum, and blood from July 2016 to November 2018 for both outpatient (OP) and IP facilities were analysed. Exclusion Criteria: No reports were excluded irrespective of age, sex, or type of specimen. The resident physician (author: SSB) downloaded the culture reports from the laboratory website by referring the patient details from a register maintained offline at the hospital in-house laboratory for whom culture testing was sent. The details of the patient's age, sex, type of specimen collected for culture, organism, and antibiotic susceptibility were taken from the lab reports, which were in PDF format. The details were copy pasted to MS-Excel, data cleaned, and analysed. Phase-1 data included: clinical history of patients, details of OP/IP, comorbidities, antibiotic resistance patterns, and antibiotic that was prescribed. Phase-2 data included only antibiotic resistance patterns, and the clinical data were not analysed in detail as the intent behind the chart audit was creating an antibiogram for the hospital.

## Comparison with ICMR data

The antibiotic resistance patterns were compared between the urban and rural sites and also to the patterns published by ICMR in their 2017 National guidelines. The 2017 guidelines were used instead of the more recent 2019, since the data collected from the above two sites were from the period 2016–2018.

## Method for developing a fishbone diagram to analyse local factors influencing antimicrobial stewardship

We examined the various factors and existing challenges that contribute to antibiotic drug mismatch by: 1) Reflecting on the process that the researchers underwent in order to collect and analyse the above data and generate the antibiogram and 2) Using the “5 Whys” approach to identify the underlying deeper hardware and software challenges in the current health system at the health care facility level. A fishbone diagram was used to represent the same.

## Results

The baseline characteristics from the two study sites are shown in Table 1.

The cultures revealed:

**Urban site:** Out of the 56 positive cultures, 27 were *Escherichia coli* (*E. coli*), 11 *Klebsiella pneumoniae* (*K. pneumoniae*), 3 pseudomonas species, 2 *Staphylococcus aureus* (*S. aureus*) and remaining 13 isolates included *Klebsiella oxytoca* (1), *Proteus*

*mirabilis* (1), *Enterococcus faecium* (2), *Salmonella typhi* (2), *Acinetobacter baumannii* (1), *Staphylococcus haemolyticus* (2), *Staphylococcus warneri* (2), and *Candida* species (2).

**Rural site:** The study included 494 patients in total from phase 1 and phase 2. Phase 1 consisted of 67 cultures that grew consisting of 21 *E. coli*, 3 *K. pneumoniae*, 5 *Pseudomonas* species isolates, 15 *S. aureus*, 7 *Streptococcus* species, and the remaining 16 isolates included 4 other *Staphylococcus* species, 1 *Proteus* species, 1 *Enterococcus faecium*, 3 *Enterococcus faecalis*, and 1 *Enterobacter cloacae*.

Phase 2 included 231 cultures that grew consisting of 66 *E. coli*, 10 *K. pneumoniae* isolates, 8 *Pseudomonas* species isolates, 55 *S. aureus*, 24 *Streptococcus* species, and remaining 68 isolates included *Proteus* species, *Enterococcus faecium*, *Enterococcus faecalis*, *Acinetobacter baumannii*, other *Staphylococcus* species, and fungal isolates. Since these organisms were not in significant numbers, we have not described them here.

## Antimicrobial resistance patterns

The antimicrobial resistance patterns in urban and rural sites are as depicted in Table 2a and 2b and are compared with the ICMR data

## Antibiotic use and mismatch

At the urban site, the de-escalation pattern was seen with 64 (43.54%) patients and escalation for 61 (41.5%), as shown in Table 3.

Table 1: Baseline Characteristics from the two study sites

Characteristics Demographics	Urban Site n (77)	Rural Phase 1 n (106)	Rural Phase 2 n (231) with NA=1
Age (Median)	45	44	Not Analysed
Male	36	59	
Female	41	47	
Patient admission details			
Out- Patient	0	22	Not Analysed
In-Patient	77	84	
Medical ward	67	84	
Surgical ward	10		
Diagnostics			
Culture testing ordered (No of Patients)	77	106	387
Total samples cultured/Culture reports	85	106	387
Sample details	n=85	n=106	n=387
a) Urine	30	51	171
b) Pus	7	44	187
c) Sputum	21	3	9
d) Blood	17	7	12
e) Miscellaneous	10	1	8
No. of sample with growth in culture	56 (65%)	67 (63%)	231 (59.6%)
Pathogen details*	n=56	n=67	n=231
	n (%)	n (%)	n (%)
a) <i>Escherichia coli</i>	27 (48.21%)	21 (31.34)	66 (28.57)
b) <i>Streptococcus Sps</i>	0 (0)	7 (10.44)	24 (10.38)
c) <i>Staphylococcus aureus</i>	2 (3.57%)	20 (29.85)	55 (31.60)
d) <i>Pseudomonas sps</i>	3 (5.35%)	5 (7.46)	8 (3.46)
e) <i>Klebsiella pneumoniae</i>	11 (19.64%)	3 (4.47)	10 (4.329)

\*Most relevant and most common pathogens

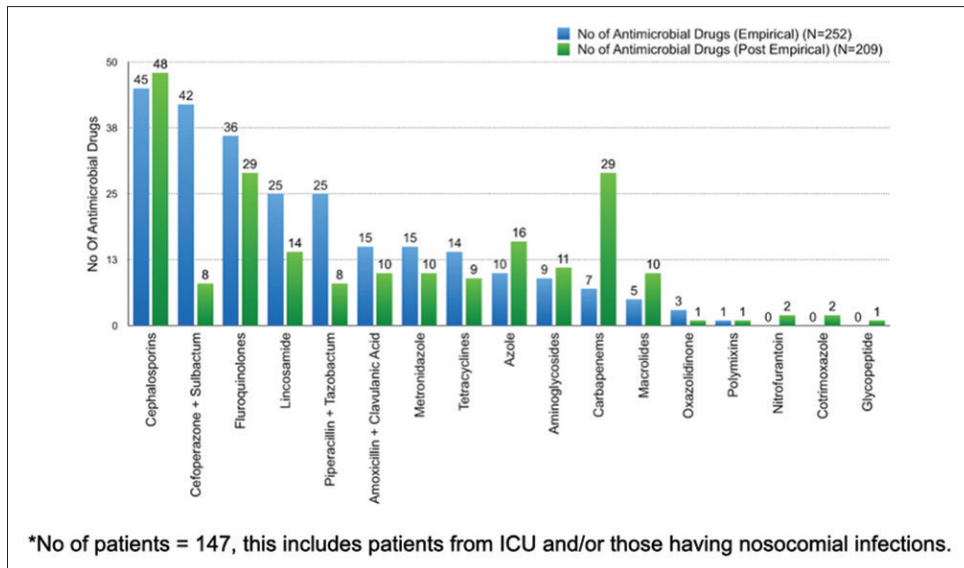


Figure 1: Pattern of antibiotic use from the urban site\*

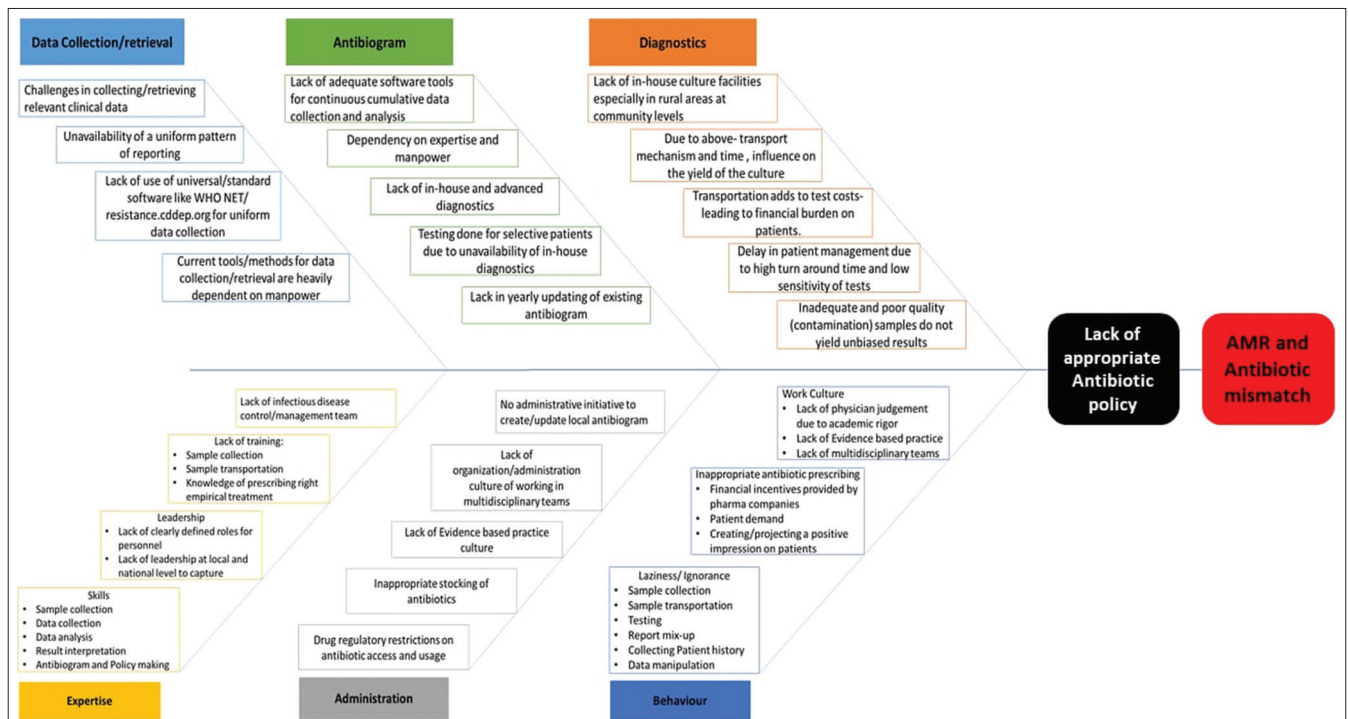


Figure 2: Fishbone diagram (root cause analysis) for antibiotic-pathogen (drug-bug) mismatch

Figure 1 describes the antibiotic use pattern in the urban site. Cephalosporins were used extensively as both empirical drugs and for escalation or de-escalation. The following reasons accounted for the escalation and de-escalations of antimicrobials: 1) culture reporting different pattern (21.69%); 2) other lab values like creatinine level, liver enzymes, etc., (12.85%); 3) significant clinical improvement (11.65%); 4) severity of symptoms (11.24%); and 5) discharge from the hospital (7.23%). Carbapenems were used in seven patients as an empirical drug, while in 29, it was given as a post empirical drug.

### The Fishbone diagram

The root cause analysis of AMR and antibiotic use mismatch is presented in Figure 2. This depicts various influencing dynamic factors towards AMR.

### Discussion

There is inadequate literature on AMR and antibiotic mismatch from India and even less literature on AMR patterns from community settings especially rural India. This paper uniquely

**Table 2a: Antimicrobial Resistance patterns among Gram negative bacteria, seen at the urban and rural sites compared with the data from AMR surveillance network Indian Council of Medical Research 2017.<sup>[9]</sup>**

Gram negative Site	<i>Escherichia coli</i> (R %)			<i>Klebsiella pneumoniae</i> (R %)			<i>Pseudomonas species</i> (R %)		
	Urban	Rural	ICMR National	Urban	Rural	ICMR National	Urban	Rural	ICMR National
No. of isolates (n)	27	87	*	11	13	*	3	13	*
Amikacin	3.7	3.45	24	9.09	33.33	54	0	8.33	35
Cefepime	74.07	32.87	79	63.63	27.27	88	33	25	41
Cefoperazone/Sulbactam	48.14	NA	33	45.45	NA	62	33	NA	NA
Ciprofloxacin	66.66	66.66	81	54.54	36.36	65	33	12.5 (n=8)	NA
Colistin	3.7	NA	1	9.09	NA	1	0	NA	10
Gentamicin	29.62	37.2	NA	45.45	25	NA	33	14.28 (n=7)	NA
Imipenem	11.11	2.74	18	27.27	27.27	35	33	25	37
Meropenem	11.11	NA	35	18.18	NA	53	0	NA	47
Piperacillin Tazobactam	44.44	19.54	43	36.36	25	68	33	16.66	46
<b>AMR pattern among rural and urban site for antibiotic for which published ICMR data is unavailable</b>									
Cefuroxime	74.07	75	NA	63.63	18.18	NA	33	NA	NA
Cotrimoxazole	44.44	35.63	NA	NA	41.66	NA	NA	NA	NA
Ceftriaxone	59.25	77.01	NA	45.45	27.27	NA	33	NA	NA
Cefixime	NA	90 (n=10)	NA	NA	NA	NA	NA	NA	NA
Nitrofurantoin	44.44	1.16	NA	72.72	45.45	NA	NA	NA	NA
Amoxycillin + Clavulanic Acid	48.14	33.33	NA	36.36	25	NA	33	NA	NA
Ampicillin	66.66	86.2	NA	63.63	100	NA	33	NA	NA

NA=not available; \*Number of isolates are not mentioned here because the ICMR guideline is defined for each antibiotic as opposed to cumulative number of isolates; R% = percentage of sample isolates resistant to the given antibiotic

**Table 2b: Antimicrobial Resistance patterns among Gram positive bacteria, seen at the urban and rural sites compared with the data from AMR surveillance network Indian Council of Medical Research 2017.<sup>[9]</sup>**

Gram positive	<i>Staphylococcus aureus</i> (R %)			<i>Streptococcus species</i> (R %)		
	Urban	Rural	ICMR National	Urban	Rural	ICMR National
No. of Isolates	2	71	*	0	31	NA
Cefoxitin (MRSA)	0	46.37	35.7	NA	NA	NA
Ciprofloxacin	100	84.28	63.3	NA	NA	NA
Clindamycin	0	32.85	25	NA	18.51 (n=27)	NA
Azithromycin	0	NA	NA	NA	47.36 (n=19)	NA
Gentamicin	0	8.57	17.8	NA	NA	NA
Linezolid	0	0	0.2	NA	0	NA
Penicillin/benzylpenicillin	50	96.36	89.2	NA	3.44	NA
Tetracycline	0	2.9	36.9	NA	29.03	NA
Cotrimoxazole	0	21.42	45.7	NA	0 (n=7)	NA
Vancomycin	0	0	0.1	NA	3.33	NA
<b>AMR pattern among rural and urban site for antibiotic for which published ICMR data is unavailable</b>						
Ceftriaxone	0	NA	NA	NA	0	NA
Levofloxacin	50	19.11	NA	NA	19.35	NA
Nitrofurantoin	100	0	NA	NA	NA	NA

Streptococcal species includes *Streptococcus pneumoniae*, but doesn't include *Enterococcus* species. \*Number of isolates are not mentioned here because the ICMR guideline is defined for each antibiotic as opposed to cumulative number of isolates. R% = percentage of sample isolates resistant to the given antibiotic R% = percentage of sample isolates resistant to the given antibiotic

adds to the literature by: a) highlighting the patterns of antimicrobial resistance at the community level; b) demonstrating a “Zoom Out” approach of looking at AMR issues; c) focusing on many hurdles faced in analysing and creating local antibiogram or local antibiotic policy, and d) suggesting a few simple solutions to address the need. We also illustrate the critical role of multidisciplinary teamwork in the collection, analysis, representation, and translation of data pertinent to AMR into clinical practice. We believe that stewardship efforts need to start in a grounded manner from “our clinic or hospital” and subsequently expand to National or Global policy.

## Significant mismatch noted between the pathogen and the antibiotic prescribed

### *Escherichia coli* and Urinary Tract Infection (UTI)

*E. coli* accounts up to 80% of the community acquired UTI, and thus is one of the most important pathogens encountered in the community.<sup>[10]</sup> The drug of choice depends on the susceptibility of *E. coli*; *Klebsiella* is also an important contributor to UTI in the community.<sup>[11]</sup>

At the urban site, Cephalosporins and Ciprofloxacin were the most common antibiotics used against UTI, but the data showed

**Table 3: De-escalation and escalation of antimicrobials at the tertiary care site**

Category	No of Patients	Percentage
De-escalation	64	43.54%
Escalation	61	41.5%
No Change	22	14.97%
Total no. of Patients	147	100%

\*No of patients=147, this includes patients from ICU and/or those having nosocomial infections.

a high percentage of resistance among *E. coli* and *Klebsiella pneumoniae* to these antibiotics. This resulted in an antibiotic mismatch and suggesting that these are suboptimal choices as empirical therapy for UTI. Better options for empirical therapy for this site could be amoxicillin + clavulanic acid, nitrofurantoin, cotrimoxazole, and gentamicin (in the hospital setting). It was good to note that colistin was seldom used and thus will remain a viable option in the near future.

At the Rural site, nearly 70% of *E. coli* were resistant to ciprofloxacin, cefuroxime, and ceftriaxone. Ciprofloxacin is the first choice drug for UTI in OP setting, and these data indicate it to be a poor first choice on account of mismatch. It is pleasant to note that *E. coli* isolates showed significantly minimal resistance to nitrofurantoin; hence, nitrofurantoin remains a good choice for uncomplicated UTI. Other oral medication options include amoxicillin + clavulanic acid and cotrimoxazole. The commonly used intravenous (IV) formulations among IPs were ciprofloxacin, ceftriaxone, and cefotaxime. These showed significant resistance. However, resistance to piperacillin + tazobactam and gentamicin was lower and these appear to be viable options for IV therapy in IPs. Carbapenems and polymyxins (colistin) were used judiciously in the facility and the resistance percentages were also low.

### Staphylococcus aureus and skin infections

At the rural site, 71 isolates were obtained mostly from pus culture of which 46.37% were MRSA. It is important to highlight here that the data from two phases of the study showed that the rate of MRSA had remained the same in both phases (approximately 50%). High resistance was seen for ciprofloxacin (84.28%) and penicillin (96.36%). Ciprofloxacin (either as oral or intravenous) and amoxicillin + clavulanic were the preferred drugs for wounds, skin, and soft tissue infections.

Ciprofloxacin does not seem to be a good drug at this site. Instead, cotrimoxazole (21.42%) might be a better choice of oral drug in these infections. Clindamycin, linezolid, and vancomycin are higher antibiotics that should be preserved for severe infections. Surprisingly, all isolates were sensitive to nitrofurantoin; hence, topical nitrofurantoin/nitrofurazone might be an option for using for local application in cases of wounds.<sup>[12]</sup> At the urban site, only two isolates were obtained and thus we have refrained from commenting on this though it is worthy to state that both were *Methicillin Sensitive Staphylococcus Aureus*.

### The problem of negative bacterial cultures

Cultures are sent with the expectation that they guide the clinician in management of their patients and it is disappointing to get a “no growth” report. In our data set as well, significant samples reported to be negative on culture (34.1% in the urban site and 39.6% in the rural site). It is interesting to note that all the blood cultures from the rural site ( $n = 19$ ) that were ordered showed no growth and 72.22% of the blood cultures ( $n = 72$ ) sent from urban site also showed no growth. This could be due to multiple reasons which are well documented in the literature<sup>[13]</sup>: low yield of blood culture (including in sepsis), transport and collection issues.

### National guidelines fail to capture the local picture of AMR: Need for hyperlocal data

The landmark document published by ICMR in 2017 on the antibiotic resistance pattern and antibiotic usage guidelines was a much needed one, but it is developed using data from four major institutes in the country and thus misses the granular data and the applicability of this in other contexts.

We make four key observations:

- 1) As illustrated by *E. coli*, the resistance to ciprofloxacin was much higher in the ICMR study (80%) as opposed to the urban and rural sites in our study (66.66%). The resistance for piperacillin + tazobactam was almost double in ICMR (43%) compared to the rural site (19.54%), but it was comparable to the urban site (44.44%). Resistance to amikacin was eight times more in the ICMR study (24%) as opposed to our sites (urban = 3.7%, rural = 3.45%). Resistance to nitrofurantoin and piperacillin + tazobactam was markedly different between the urban (higher resistance) and rural (lower resistance) sites, making nitrofurantoin a better suited for the rural setting, although ICMR guidelines fail to comment on nitrofurantoin sensitivity patterns.
- 2) Additionally, it is important to note that though the overall resistance rates might be higher at urban sites, for certain other antibiotics, resistance at rural sites might be higher, e.g., resistance among *Klebsiella* spp to Amikacin (9.09% urban vs. 33.33% rural). This highlights the fact that antibiotic resistance burden exists in all settings, and the patterns are specific to each local setting and time period.
- 3) Unexpectedly, *Staphylococcus aureus* resistance between the rural site and ICMR showed that the resistance was higher in the rural site compared to ICMR for ciprofloxacin (84.28% vs 63.3%) and clindamycin (32.85% vs 25%). This highlights the fact that the “one size fits all” rule does not apply to antibiotic policy and we cannot assume that rural patterns would be better than urban or national data.
- 4) The above observations indicate that having an antibiogram and antimicrobial stewardship program becomes more effective when driven locally. However, creating and updating a local antibiogram and antibiotic policy is complex in both urban and rural settings. Some of the challenges as noted in

previous studies are: infrastructural constraints, significant patient load,<sup>[14]</sup> lack of orientation and training, diagnostics, and strong political commitment.<sup>[15]</sup> Going forward, there is a need to streamline the processes of data collection locally to predict AMR trends and facilitate AMR stewardship. Additionally, adapting better technological tools for data collection, continuous analysis, and periodic updation will facilitate translation of antibiogram data into clinical practice.

### Study limitations

1. Sampling bias: The practice of ordering a bacterial culture is not uniform. Ordering a test is influenced by factors such as unresolving infection, “difficult to treat” infections, who is treating and affordability. On account of these real-world challenges, one should bear in mind that the patterns obtained may differ from the true antimicrobial resistance patterns prevalent in a given setting.
2. While bacteriological data were available, clinical correlation could not be done. As a result, unique patterns among patient subgroups such as those with Diabetes, HIV, etc., could not be determined.

### Conclusion: Lessons learned

- This paper highlights the distinct patterns and burden of AMR in urban and rural settings and compared it to national level data.
- The role of community-based primary care practices in antimicrobial stewardship is irrefutable and hence strives to have local antibiotic policies.
- One of the main barriers to the above-mentioned practice is the lack of access to culture facilities in resource limited settings, adequate technology tools, and expertise as depicted in the fishbone diagram.
- One way around these challenges is aggregating demand for microbiology services by bringing smaller clinics, Primary Health Centres, and rural hospitals together and linking them with a common microbiology laboratory and shared data platforms to facilitate antibiotic stewardship at the community level.
- At a national level, there is a need for integrating these processes to facilitate the local efforts and navigate the challenge of AMR.

### Key Messages

- 1) The burden of AMR is high in both rural and urban sites, reinforcing that AMR burden cannot be ignored in rural settings.
- 2) Mechanisms of linking rural practices, primary health centres, and small hospitals with a common microbiology laboratory and shared data platforms will facilitate antibiotic stewardship at the community level.

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### Conflicts of interest

There are no conflicts of interest.

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