

Knowledge, attitudes and practices related to the use of oral cephalosporins in community-acquired pneumonia in India



Sanket Sawant¹, Krunal Dalal², Ramiya Ravindranath³, Puja Nijhara⁴

^{1,2}Medical Affairs, GSK, Mumbai, ³Department of Statistics, GSK, Bengaluru, ⁴Global Medical Affairs, GSK, Mumbai, India

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is a leading cause of mortality and morbidity and requires extensive antibiotic treatment. **Aims and Objectives:** This study aimed to understand the knowledge, attitudes, and practices (KAP) of consulting physicians in treating CAP. **Materials and Methods:** A cross-sectional, descriptive KAP study surveyed 250 consulting physicians treating CAP from metro, tier-1, and tier-2 cities in India. A web-based questionnaire with 7 main questions was used to collect data between August and September 2024. **Results:** Of the 250 physicians enrolled in the study, *Streptococcus pneumoniae* was identified by 74% of physicians as the most common cause of CAP, followed by *Haemophilus influenzae* (49.2%), across all zones. Most physicians (89.6%) scored 50–79% on CAP knowledge questions, indicating moderate knowledge. Most physicians (94%) highlighted the need to regularly update knowledge for CAP. Clinical experience was relied upon by 54.6%, 32% disagreed, and 13.4% remained neutral. Majority (89.2%) viewed antibiotic resistance as a major concern, and 87.6% agreed treatment should target *S. pneumoniae*. 61.6% were concerned about increased side effects from cephalosporin–clavulanic acid combinations. Patient compliance was a key factor for 91.6%, with 79.2% preferring simpler dosing regimens. In the survey, 82% followed moderately accurate practices (50–79%) for managing CAP, including diagnostics, risk assessment, and antibiotic selection. However, 17.2% demonstrated poor accuracy, scoring below 50%. **Conclusion:** This study identified current practices and possible gaps in appropriate antibiotic prescribing for CAP. Targeted education programs on rational antibiotic use can be an effective strategy to strengthen antimicrobial stewardship and combat resistance in India.

Key words: Community-acquired pneumonia; Antimicrobial resistance; Antibiotic stewardship; Knowledge, attitudes, and practices; Cephalosporins

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INTRODUCTION

Antimicrobial resistance (AMR) is a significant global health threat, linked to 1.27 million deaths and contributing to 4.95 million deaths in 2019.¹ In 2019, India reported 297,000 deaths directly attributable to AMR and 1,042,500 deaths associated with it.² *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are the leading

pathogens, with around 200,000 deaths caused by drug-resistant strains.³ Overusing antimicrobials can lead to drug-resistant bacteria, so careful use is essential.^{1,4}

Acute respiratory tract infections are a leading cause of adult antibiotic prescriptions, often inappropriately, further fuelling AMR.⁵ Lower respiratory tract infections (LRTIs) are the leading infectious disease linked to AMR mortality, with 1.5 million fatalities and an incidence of

Address for Correspondence:

Dr. Sanket Sawant, Anti-Infectives and Pain, Global Medical, GlaxoSmithKline, Mumbai, India. **Mobile:** +91-9987313338.

E-mail: sanket.x.sawant@gsk.com

23.17 deaths/100,000.^{2,3} Community-acquired pneumonia (CAP) is the most common form of LRTIs and a major cause of mortality and morbidity, with clinical and economic impacts.^{6,7} CAP treatment depends on its severity: mild cases are managed outpatient, moderate cases in hospitals, and severe cases in intensive care units.^{8,9} In outpatient settings, confirming the diagnosis before treatment is crucial. In India, *S. pneumoniae* remains the leading cause of CAP, followed by *K. pneumoniae*, and *L. pneumophila*. Given its prevalence, targeting *S. pneumoniae* is a critical focus in the management and treatment of CAP.¹⁰ The Indian Council of Medical Research (ICMR) recommends amoxicillin-clavulanic acid as the treatment of choice; alternative treatments include macrolides and cephalosporins for outpatients without comorbidities.¹¹ For patients with comorbidities, combination therapy with amoxicillin-clavulanic acid and macrolide/doxycycline is indicated. For inpatients, the aim is to cover atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp.), provide immunomodulation, and reduce mortality.¹¹ Fixed-dose combinations (FDCs) can improve effectiveness and adherence, but many, like cephalosporins with clavulanic acid labelled “discouraged” by the World Health Organization (WHO), are still widely used in India.^{12,13} Despite the availability of clear guidelines for the management of CAP, practice often deviates from guidelines.¹² A study highlighted cefixime as the most used cephalosporin (31%) despite not being guideline-recommended, revealing a gap between practice and recommendations.¹⁴ Furthermore, antibiotic consumption data from India indicate overuse of broad-spectrum third-generation cephalosporins.¹⁵ This overuse may stem from improper prescriptions or over-the-counter sale of antibiotics, highlighting the need for stricter regulations and stewardship programs.¹² In addition, health system factors may influence prescribing practices, with some providers influenced by external incentives tied to treatment decisions.¹⁶

Despite established guidelines for CAP management in India, real-world prescribing practices often diverge, particularly with oral cephalosporins and their FDCs. Limited adherence to evidence-based recommendations and variability in physician knowledge and attitudes contribute to inappropriate antibiotic use and rising AMR. Addressing these knowledge gaps is essential to promote rational prescribing, align clinical practice with national and global CAP management protocols, and mitigate the growing public health threat of AMR. Therefore, this survey was designed to evaluate the knowledge, attitudes, and practices (KAP) of Indian physicians when prescribing oral cephalosporins or their FDCs for the treatment of CAP. This may help to further define the problem of inappropriate antibiotic use in CAP to support the

implementation of precise measures promoting rational use of antibiotics and further contribute toward the mitigation of AMR.

Aims and objectives

This survey evaluated the knowledge, attitudes, and practices (KAP) of Indian physicians when prescribing oral cephalosporins or their FDCs for the treatment of CAP.

MATERIALS AND METHODS

Study design

A descriptive cross-sectional survey was conducted between August-2024 to September-2024 with targeting at least 250 consulting physicians across India from metro, tier-1 and tier-2 cities (4 cities/zone), covering all four zones, to assess the KAP related to the use of oral cephalosporins monotherapy or FDCs for the management of CAP in India. Cities were strategically selected to ensure diverse healthcare representation, enabling broader applicability of findings and accounting for regional differences in CAP management. The primary objectives of the study were to determine:

- The percentage of consulting physicians who can accurately identify the likely pathogen, resistance patterns, severity of disease, generation of cephalosporin, specific bacterial coverage, antibiotic susceptibility, and usage of oral cephalosporins and FDCs for CAP
- The percentage of consulting physicians expressing favorable attitudes towards the use of oral cephalosporins and their FDCs by identifying specific factors influencing their choice, such as guideline recommendation, resistance development, patient compliance, safety, and perceived efficacy
- The consulting physicians' adherence to guidelines or protocols in prescribing and administering oral cephalosporins and their FDCs by assessing the percentage of prescribed instances of these antibiotics that align with recommended practices for CAP.

The face-to-face computer-assisted personal interviewing (CAPI) technique was used to conduct the survey and ensure data integrity and accurate self-reporting. Participants were blinded to the sponsor to minimize bias and were paid an honorarium aligned to the fair market value. Data were reviewed for completeness and validity, and incomplete responses were excluded. This approach helped maintain high response reliability and minimized entry errors throughout the survey process.¹⁷

The study was approved by the Royal Pune Independent Ethics Committee (registration no. ECR/45/Indt/

MH/2013/RR-19) in India.

A detailed description of questionnaire development and validation is included in the Supplementary material.

Study population and sample size

Potential responders were randomly selected by a trusted third-party vendor in the study's target countries. Physicians were eligible if they:

- Practice in India, spending at least 70% of their time in patient care
- Work in specific cities (Metro: Mumbai, Delhi, Kolkata, Chennai; Tier-1: Ahmedabad, Lucknow, Patna, Calicut; Tier-2: Rajkot, Chandigarh, Guwahati, Madurai)
- 5 and 30 years of experience
- Treat at least 3 cases of CAP in the month before the survey
- Use oral cephalosporins for managing CAP
- Willing to provide informed consent.

Detailed inclusion and exclusion criteria are summarized in Supplementary Table S1.

The sample size was calculated using Raosoft Web. Given the study's descriptive nature, the sample size was based on logistical considerations to provide reasonable estimates for primary and secondary outcomes. With no prior data, it was hypothesized that the correct response distribution would likely be between 60% and 90%, with 70% and 80% being more plausible. A sample size of 250 was considered feasible. Supplementary Table S2 shows the expected margin of error (at a 95% confidence interval) for various response distribution levels (50–90%) for sample sizes between 100 and 400 responders.

Online survey distribution and data collection

The study protocol, informed consent form (ICF), and questionnaire were approved by the Central Independent Ethics Committee. Eligible physicians gave consent before participating. The ICF clarified that participation was voluntary, and responses would remain confidential.

Data analysis

Statistical analyses were explorative and descriptive, using R software (version 4.3.1 or higher). Demographic data were presented as counts and percentages, while quantitative responses were shown in tables and graphs. A 5-point Likert scale assessed knowledge, with scores assigned based on correct and incorrect answers. The questionnaire included both correct and incorrect statements to evaluate knowledge and practice. Scores ranged from 0 to 21 for knowledge and 0 to –14 for practice. Mean (standard deviation [SD]) scores were presented, and overall knowledge was categorized into three groups: >80%

(mostly accurate), 50–79% (partially accurate), and <50% (mostly inaccurate). Individual knowledge scores were computed as percentages, ranging from 0% to 100%. The overall attitude of physicians was summarized using counts and percentages of responses.

RESULTS

Demographics and participant characteristics

Of the 250 physicians enrolled in the study, 110 were from metro cities, 80 were from tier-1, and 60 belonged to tier-2 cities.

Knowledge of participants

Most physicians suggested *S. pneumonia* (74%) and *H. influenzae* (49.2%) as the common organisms responsible for CAP. *S. pneumoniae* was the most common CAP pathogen across all zones (Figure 1).

Most physicians (89.6%) had moderate CAP knowledge (50–79% scores). This was highest in tier-1 cities (93.8%), followed by metros (91.8%) and tier-2 cities (80%). The average score was 12.4 (SD 1.75), with tier-2 cities scoring significantly lower compared to metros ($P=0.0252$) and tier-1 cities ($P=0.0137$) (Table 1).

Beliefs of consulting physicians

The majority (overall: 94%; strongly agree: 53.6%, agree: 40.4%) of physicians emphasize the importance of regularly updating knowledge about antibiotic use in CAP. While a majority of participating physicians (54.6%) believed that clinical experience alone is sufficient for deciding on antibiotics for CAP, a notable proportion (32%) disagreed with this notion.

Most physicians (89.2%) agreed that antibiotic resistance was a major concern in CAP management. Most believed (87.6%) that antibiotic therapy in CAP should target

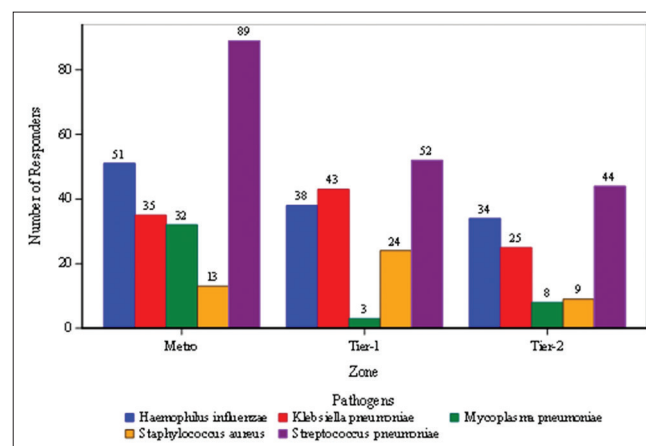


Figure 1: Pathogens commonly associated with CAP by zone (n=250)

Table 1: Consulting physicians' knowledge by zone (n=250)

Zone	Scores category	n (%)
Metro (n=110)	<50	9 (8.2)
	50–79	101 (91.8)
	≥80	0 (0)
Tier-1 (n=80)	<50	5 (6.3)
	50–79	75 (93.8)
	≥80	0 (0)
Tier-2 (n=60)	<50	12 (20.0)
	50–79	48 (80.0)
	≥80	0 (0)

P-value (metro vs. tier-1)-0.6148, P-value (metro vs. tier-2)-0.0252, P-value (tier-1 vs. tier-2)-0.0137

“*Streptococcus pneumoniae*”, a common pathogen responsible for CAP. Most physicians (84.4%) also agreed that second and third-generation oral cephalosporins provide adequate coverage for CAP, and 90% of the physicians agreed that clavulanic acid reduces the minimum inhibitory concentration (MIC) of cephalosporins against common CAP pathogens. A strong positive opinion (91.2%) was noted regarding the addition of clavulanic acid, linked with the improvement of efficacy of cephalosporins in CAP management. However, majority (61.6%) believed that the use of cephalosporin FDCs with clavulanic acid may increase the adverse effects in patients.

Most physicians (77.6%) believed that FDCs of cephalosporins are supported by guidelines for managing CAP. A clear majority (91.6%) believed that the patient compliance should be a key consideration when choosing antibiotics for CAP, highlighting the importance of patient-centred care. Amoxicillin–clavulanic acid 1 g BD (twice daily) was more conducive to patient compliance than 625 mg 3 times daily, according to 79.2%, suggesting a preference for simpler dosing regimens. The attitudes and beliefs of the physicians are summarized in Table 2. Zone-wise distribution is presented in Supplementary Table S3.

Practices followed by consulting physicians

In the survey, 82% of physicians reported moderately accurate practices for CAP management, while 17.2% reported inaccurate practices. Accuracy was highest in tier-1 cities (90%) and lowest in tier-2 cities (70%), where inaccurate practices were most common (28.3%). The tier-1 versus tier-2 difference was statistically significant ($P=0.0044$) (Table 3).

Factors considered while deciding on oral antibiotics for the management of CAP

For most physicians (70%), “severity of diseases” was crucial for antibiotic selection, followed by “presence of co-morbidities” (65.6%), “bacterial coverage of the antibiotic” (51.2%), and “patient compliance” (50%).

Physicians emphasized disease severity, presence of comorbidities, bacterial coverage, and patient compliance in all regions. Guideline recommendations, patient affordability, and drug efficacy profile were important considerations for metro, tier-1 and tier-2 cities (Supplementary Table S4).

Factors considered while deciding on oral cephalosporins for the management of CAP

For prescribing oral cephalosporins, 72.8% of physicians expressed that “severity of disease” was an important factor, followed by “presence of co-morbidities” (59.2%), and “bacterial coverage of antibiotic” (56.4%). Drug safety profile (45.6%) was given more importance than “patient compliance” (43.6%) (Supplementary Table S5).

Barriers leading to poor compliance with CAP guidelines or protocols among consulting physicians

Fear of poor outcomes with narrow-spectrum antibiotics (42.4%), patient compliance (38.4%), and lack of familiarity with guidelines (36%) were substantial barriers to adherence to CAP guidelines or protocols. Poor accessibility (28.4%), conflicting guidelines (23.6%), and lack of time to stay updated (23.6%) were additional barriers reported (Supplementary Table S6).

Knowledge sources that have the highest impact on treatment approaches and practices

The three main knowledge sources reported were “medical conferences/CMEs/webinars”, “national/international guidelines” and “medical journals” (Supplementary Table S7).

DISCUSSION

The study offers detailed insights into physicians' KAP regarding oral cephalosporin monotherapy or FDCs for CAP management in India. Practices were consistent across regions, and the sampling ensured broad representation, supporting generalization of the findings nationwide.

S. pneumoniae was identified to be the most common causative agent associated with CAP, followed by *H. influenzae*, *K. pneumoniae*, *S. aureus*, and *M. pneumoniae*, as is consistent with established evidence from India. A systematic review by Vikhe et al., reported *S. pneumoniae* in 33% of CAP cases, followed by *K. pneumoniae*, *S. aureus*, *M. pneumoniae*, *L. pneumophila*, *C. pneumoniae*, *H. influenzae*, and *P. aeruginosa*.¹⁸ Another study found *S. pneumoniae* in 19% of cases, reinforcing its role as a leading pathogen.¹⁰ However, a study by Yadav et al., in North India, revealed *K. pneumoniae* as the most common isolate, followed by *E. coli*, with *S. pneumoniae* present in only 5% of cases.¹⁹ These variations highlight the regional differences in CAP

Table 2: Summary of consulting physicians' attitudes and beliefs (n=250)

Parameter	Strongly disagree n (%)	Disagree n (%)	Neither agree nor disagree n (%)	Agree n (%)	Strongly agree n (%)
Update knowledge regularly on the usage of antibiotics for the management of CAP	1 (0.4)	1 (0.4)	13 (5.2)	101 (40.4)	134 (53.6)
Only clinical experience is sufficient to decide antibiotic for the treatment of CAP	38 (15.2)	42 (16.8)	31 (12.4)	70 (28.0)	69 (27.6)
Antibiotic resistance is a significant issue in CAP management	-	10 (4.0)	17 (6.8)	109 (43.6)	114 (45.6)
Overall antibiotic therapy should be geared towards covering <i>Streptococcus pneumoniae</i> in CAP	1 (0.4)	3 (1.2)	27 (10.8)	116 (46.4)	103 (41.2)
Second and third generation oral cephalosporins have adequate bacterial coverage for CAP	3 (1.2)	9 (3.6)	27 (10.8)	125 (50.0)	86 (34.4)
Addition of clavulanic acid results in a decrease in the MIC of cephalosporins (such as cefuroxime) against common CAP pathogens	-	4 (1.6)	21 (8.4)	126 (50.4)	99 (39.6)
Addition of clavulanic acid to oral cephalosporins improves the efficacy of cephalosporins in CAP	-	2 (0.8)	20 (8.0)	114 (45.6)	114 (45.6)
Use of cephalosporin FDCs with clavulanic acid may increase the adverse effects in patients.	18 (7.2)	40 (16.0)	38 (15.2)	93 (37.2)	61 (24.4)
FDCs of cephalosporins are endorsed by guidelines for the effective management of CAP	11 (4.4)	13 (5.2)	32 (12.8)	130 (52.0)	64 (25.6)
Patient compliance is an important factor to be considered while selecting an antibiotic	-	3 (1.2)	18 (7.2)	108 (43.2)	121 (48.4)
Amoxicillin-clavulanic acid 1 g BD provides better patient compliance than amoxicillin-clavulanic acid 625 mg TDS in CAP management	11 (4.4)	14 (5.6)	27 (10.8)	118 (47.2)	80 (32.0)

CAP: Community-acquired pneumonia, BD: Twice daily, TDS: Three times a day, FDC: Fixed-dose combination, MIC: Minimum inhibitory concentration, FDCs: Fixed-dose combinations, MIC: Minimum inhibitory concentration

Table 3: Summary of consulting physicians' practice by zone (n=250)

Zone	Scores category (%)	n (%)
Metro (n=110)	<50	19 (17.3)
	50-79	91 (82.7)
	≥80	0 (0)
Tier-1 (n=80)	<50	7 (8.8)
	50-79	72 (90.0)
	≥80	1 (1.3)
Tier-2 (n=60)	<50	17 (28.3)
	50-79	42 (70.0)
	≥80	1 (1.7)

P-value (metro vs. tier-1)-0.0868, P-value (metro vs. tier-2) - 0.0597, P-value (tier-1 vs. tier-2) - 0.0044

aetiology across India. Therefore, it is crucial for physicians to regularly access local data on prevalent pathogens and their antibiotic sensitivity patterns to guide effective treatment and improve patient outcomes.

Most participants, particularly physicians in tier-1 cities (67.6%), reported that they rely on their years of clinical experience. Previous studies suggested that empirical therapy may be initiated in patients with suspected CAP; however, appropriate adjustments must be made once culture and sensitivity reports are made available.^{20,21} Interestingly, empirical treatment for CAP has been shown to be associated with increased AMR.⁽²¹⁾ Hence, while clinical experience is important for early identification and treatment of CAP, it is important to strategize the

use of specific antibiotics against identified pathogens to limit AMR.

Majority of physicians in this survey agreed that second and third-generation oral cephalosporins provide adequate coverage for CAP, with the use seen more among physicians in metros than tier-1 and 2 cities, consistent with the high percentage of cephalosporin use reported in Indian studies.^{22,23}

Most physicians agreed that adding clavulanic acid enhances cephalosporin efficacy in CAP by lowering MIC against common pathogens. However, a notable divergence or neutrality was observed among physicians in metro areas (32.8%) and tier-2 cities (20%). Clavulanic acid is generally not combined with cephalosporins like cefuroxime, as these drugs are naturally stable against common beta-lactamases. Therefore, adding clavulanic acid offers no clear scientific or therapeutic benefit.^{12,24} Around 80% of antibiotic use in LMICs occurs in community settings with limited stewardship. The UNGA recommends that 70% of antibiotic consumption should be from the "Access" group. Thus, tracking prescribing trends and promoting appropriate access to antibiotic use is key to improving CAP management and curbing AMR.²⁵ In India, there is a notable discrepancy between recommended guidelines and actual prescribing practices for CAP.²⁶ Although amoxicillin-clavulanate is advised in cases with comorbidities, and cefuroxime or cefpodoxime for uncomplicated CAP, many

physicians opt for unapproved combinations. Notably, 77.6% of surveyed physicians believed cephalosporin-clavulanic acid FDCs are guideline-supported, despite the WHO listing them as “discouraged.”¹² While 61.6% of physicians expressed safety concerns about cephalosporin-clavulanic acid FDCs, metro-based doctors were more likely to prescribe them. This disconnect between awareness and practice highlights the urgent need for nationwide training and strict adherence to CAP management guidelines.

This also underscores a gap in understanding the pharmacological mechanisms of antibiotics, emphasizing the importance of educating physicians on the pharmacokinetics and pharmacodynamics of these agents. In addition, the divided opinions on the safety profile of cephalosporin-clavulanic acid combinations highlight the necessity for further education on their adverse effects and prevalence in patients. Addressing this issue requires ongoing engagement with consulting physicians, ensuring they are kept up to date with the latest guidelines and preferred antibiotic regimens.

Most participants were compliant with appropriate practices for CAP management. Physicians reported discomfort using narrow-spectrum antibiotics as they may lead to poor outcomes. This prevented them from following the recommendations of the guidelines for treating CAP. Other barriers to compliance were a lack of familiarity (36%) and poor access (28.4%) to guidelines. Though participants were confident in the credibility of the peers who developed the guidelines, a considerable number of them did not have access or the time to stay updated (23.6%). Physicians in the metro felt there were conflicting guidelines (30.9%), and tiers 1 and 2 had issues with poor accessibility.

To strengthen the clinical relevance of these findings, periodic review of CAP management guidelines in collaboration with the ICMR and regional health bodies to reflect evolving resistance patterns and emerging data is recommended. Through structured workshops, webinars, education programs on antibiotic stewardship, and updated CAP protocols, medical associations may bridge certain gaps. These initiatives would promote consistent, evidence-based prescribing and support the rational use of access antibiotics. Such collaborative efforts are key to translating research into practice and addressing the growing AMR threat in India.

This study has several strengths. We recruited physicians with 5–30 years of experience who dedicate at least 70% of their time to treating CAP, reducing recall bias. The CAPI methodology further ensured spontaneous responses by limiting online searches or influence from later questions.

A comprehensive, quantitative questionnaire developed through an extensive literature review was used to assess physicians’ knowledge. The findings highlight a clear need for targeted training materials to support appropriate antibiotic selection.

Our study has certain limitations. The surveyed physicians were from diverse cities with varying healthcare infrastructures and insurance landscapes, which may influence differences in beliefs across metro, tier-1, and tier-2 cities. All responses were self-reported and not independently validated, which may impact data accuracy. The subjective nature of the survey also affects the reliability of measuring physicians’ attitudes. In addition, the findings may have temporal limitations and may not be replicable if the survey is repeated at a different time.

CONCLUSION

This survey involved 250 physicians across India to evaluate their KAP regarding the prescription of oral cephalosporins or their FDCs for treating CAP. *S. pneumoniae* was the most common pathogen, followed by *H. influenzae*. Physicians in metropolitan areas had better knowledge scores than those in tier-2 cities. Most physicians found it crucial to stay updated on antibiotic use and relied on guidelines, conferences, and webinars. Medical representatives were a key source in tier-2 cities, while local trial data was generally not preferred. Over half of the physicians also depended on their clinical experience for prescribing decisions. Physicians across regions believed second and third-generation oral cephalosporins were effective for CAP. Many believed adding clavulanic acid reduced the MIC of cephalosporins, a view more common in metro and tier-1 cities, despite a lack of scientific rationale and being labelled as “discouraged FDCs” by WHO. However, there were concerns regarding the adverse effects of these FDCs. This highlights the need for tailored educational programs for these physicians.

Practice adequacy was moderate, with some physicians not fully following guidelines due to concerns of poor outcomes, unfamiliarity with guidelines, time constraints, and poor accessibility. Although many recognized the need to update their knowledge, this often did not lead to changes in practice. The study emphasizes that a solid understanding of antibiotic pharmacokinetics and resistance mechanisms is crucial for appropriate prescribing. Findings highlight a clear need for enhanced physician education in India, particularly on the proper use of oral cephalosporins and their FDCs in CAP management to improve patient outcomes and help reduce AMR driven by antibiotic misuse.

This study highlights critical gaps in CAP management, emphasizing the need for continuing education to align clinical practice with evidence-based guidelines. Targeted CME programs on rational antibiotic use can play a vital role in strengthening stewardship efforts and combating AMR in India.

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DATA AVAILABILITY

All relevant data for this research are present in the manuscript and supplementary files.

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Authors' Contributions:

SS- Conceptualization, data curation, formal analysis, funding, methodology, project administration, resources, software, supervision, validation, visualization, writing - original draft, and writing - review and editing; **KD-** Methodology, validation, visualization, writing - original draft, and writing - review and editing; **RR-** Formal analysis, funding, methodology, validation, visualization, writing - original draft, and writing - review and editing; **PN-** Data curation, formal analysis, methodology, validation, visualization, writing - original draft, and writing - review and editing; All authors contributed to methodology, validation, visualization, writing - original draft, and writing - review and editing and had access to full data sets. SS also contributed to conceptualization, data curation, formal analysis, funding, project administration and resources.

Work attributed to:

GSK India.

Orcid ID:

Sanket Sawant -  <https://orcid.org/0000-0002-5825-5116>

Krunal Dalal -  <https://orcid.org/0000-0001-5189-7469>

Ramiya Ravindranath -  <https://orcid.org/0009-0001-0960-0200>

Puja Nijhara -  <https://orcid.org/0000-0001-9931-1658>

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