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Original Article

Microbiology Section

Antimicrobial Susceptibility Patterns of *Haemophilus influenzae* and *Streptococcus pneumoniae* in Respiratory Tract Infections: A Retrospective Observational Real-world Database Study in India

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ABSTRACT

Introduction: Antimicrobial Resistance (AMR) presents a major worldwide challenge to public health, leading to significant levels of illness and death in India. The rise in antibiotic prescriptions during the pandemic raised concerns over the possible increase in antibiotic resistance and the risk of AMR.

Aim: To investigate the real-world antibiotic susceptibility patterns of *Haemophilus influenzae* and *Streptococcus pneumoniae* to various antibiotics using diagnostic laboratory-based Antibiotic Sensitivity Testing (AST) data from India.

Materials and Methods: This was a retrospective, observational, real-world database study that included 1,351 diagnostic AST records of the most common respiratory specimens collected from all ages between January 2017 and July 2022. Diagnostic AST records were collected across four accredited diagnostic laboratories in India, selected through an exhaustive Quality Control (QC) process validated by microbiology experts. The susceptibility patterns of *H. influenzae* and *S. pneumoniae* to amoxicillin-clavulanic acid, azithromycin, levofloxacin, cefixime, cefpodoxime and cefuroxime were evaluated using quantitative analysis {mean±standard deviation, median (range) for age, frequency and proportions; and Odds Ratios (OR) comparing the susceptibility patterns of amoxicillin-clavulanic acid with other antibiotics} and reported as per the standard AST results as % Sensitive, % Intermediate and % Resistant.

Results: Of the 1,351 diagnostic AST records included in the analysis, 1,257 (93.0%) were from adults (≥18 years). Most *H. influenzae* {566/608 (93.1%)} and *S. pneumoniae* {554/743 (74.6%)} isolates were from sputum samples. Most isolates of *S. pneumoniae* {227 (95.8%)} and *H. influenzae* {86 (88.7%)} were susceptible to amoxicillin-clavulanic acid. Susceptibility to amoxicillin-clavulanic acid was higher compared to most of the antibiotics evaluated. *S. pneumoniae* also showed high susceptibility to second-generation {cefuroxime: 87.4% (n=111)} and third-generation cephalosporins {cefixime: 91.3% (n=115), cefpodoxime: 97.5% (n=119)}. The susceptibility patterns of both organisms remained consistent during the pre- and post Coronavirus Disease-2019 (COVID-19) pandemic periods, except for *H. influenzae* to cefixime {94.0% (n=252) to 63.7% (n=137)}.

Conclusion: The overall susceptibility patterns of *H. influenzae* and *S. pneumoniae* to the selected antibiotics varied over the 5-year study period. The susceptibility of both organisms to amoxicillin-clavulanic acid remained high with some fluctuations. This data also guides clinicians in making evidence-based decisions for managing Respiratory Tract Infections (RTIs).

Keywords: Antibiotic sensitivity testing, Antimicrobial resistance, Retrospective studies

INTRODUCTION

AMR presents a significant threat to human health, with the World Health Organisation (WHO) recognising AMR as one of the top ten global public health challenges [1]. The burden of bacterial AMR has been associated with 4.95 million (3.62-6.57 million) deaths in 2019, including 1.27 million (95% uncertainty interval, 0.911-1.71) deaths attributable to bacterial AMR [2].

Even in lower-middle-income countries like India, AMR is a prevalent issue causing an increase in morbidity and mortality rates, as well as longer hospital stays, further adding to the healthcare expenditure of the state [3,4]. India reported a high usage of antibiotics between 2010 and 2020, at 30.6% per capita, which has been linked to AMR [5]. Therefore, India framed the National Action Plan on AMR 2017-2021, which laid down guidance for appropriate antibiotic use [6]. In addition, guidelines have also been published by the National Centre for Disease Control (NCDC) and the Indian Council of Medical Research (ICMR) to ensure appropriate antibiotic use [3,7].

The global COVID-19 pandemic further added a concerning dimension to the AMR challenge, where a high prevalence of antibiotic prescriptions (74.6%) was reported in COVID-19 patients, even though the bacterial co-infection rate was merely 8.6% [8]. Another study by Raychaudhuri D et al., reported antibiotic prescriptions in 88.3% of children in India with COVID-19 and bacterial co-infection [9]. During India's first pandemic phase, a significant rise in azithromycin prescriptions raised concerns about an increased risk of AMR [10].

In India, infectious diseases are widespread; the most commonly reported are RTIs, which have a high mortality rate [11]. In 2018, the National Health Portal of India recorded 41,996,260 RTI cases and 3,740 deaths [12]. Notably, lower RTIs were the leading cause of death in India in 2019 [12]. *Streptococcus pneumoniae* and *Haemophilus influenzae* are common commensal bacteria inhabiting the nasopharynx of healthy humans and causing various infections, including RTIs. The WHO identified *S. pneumoniae* and *H. influenzae* on the global priority pathogen list for which new

antibiotics are needed, demonstrating susceptibility patterns that vary considerably, both over time and regionally [13,14].

With the alarming rise in AMR in India and the consumption of antibiotics for RTI management contributing to it, it is important to generate antibiotic susceptibility data against the key pathogens causing RTIs. Unfortunately, there is scarce information regarding these pathogens and their susceptibility trends in India. This retrospective observational real-world database study was conducted to investigate the real-world antibiotic susceptibility patterns by using diagnostic laboratory-based AST data over a five-year period in India. Six antibiotics, namely, amoxicillin-clavulanic acid, azithromycin, levofloxacin, cefixime, cefpodoxime and cefuroxime, were selected based on the NCDC and ICMR treatment guidelines for RTIs [3,7,15,16]. The primary study outcome was to evaluate the overall susceptibility patterns of *H. influenzae* and *S. pneumoniae* to amoxicillin-clavulanic acid, azithromycin, levofloxacin, cefixime, cefpodoxime and cefuroxime. The secondary outcomes included assessing year-wise temporal trends by comparing the susceptibility patterns of *H. influenzae* and *S. pneumoniae* to the antibiotics, evaluating susceptibility across age groups (adults and children), and states/zones (regions of India-North, West, East, South, and Central), as well as comparing antibiotic susceptibility trends for samples before and after the COVID-19 pandemic (2017-2019 versus 2020-2022).

Findings from this study are expected to address the current evidence gaps in antibiotic susceptibility trends of common respiratory pathogens in India and assist clinicians in making evidence-based decisions for managing RTIs.

MATERIALS AND METHODS

This study was a retrospective real-world database analysis. The specimen samples included in the study were collected between January 2017 and July 2022. This study complied with the tenets of the Declaration of Helsinki and was approved by an Independent Ethics Committee (IEC), specifically the Royal Pune Independent Ethics Committee (RPIEC), India, which issued an approval letter dated December 14, 2022, for Metropolis Healthcare Ltd., Mumbai, India (RPIEC141222); SRL Limited, Gurgaon (RPIEC180123), which issued an approval letter dated January 18, 2023; and Tenet Medcorp Pvt. Ltd., Telangana (RPIEC 221222), which issued an approval letter dated December 22, 2022, along with the Institutional Ethics Committee at Max Super Specialty Hospital, New Delhi, India (BHR/RS/MSSH/MHIL/SKT-1/MHEC/IM/23-01), which issued an approval letter dated January 30, 2023. An informed consent waiver was obtained from all the ethics committees, considering the minimal risk associated with this research and that the waiver would not adversely affect the rights and welfare of the study participants.

Inclusion criteria: For diagnostic laboratory records to be included in the study, all of the following inclusion criteria must have been met:

- Specimen test date within the five-year period (January 2017 - July 2022);
- Age information available (all ages were eligible);
- *H. influenzae* and/or *S. pneumoniae* isolated from the following specimens: blood (only in the case of children), throat swab, bronchoalveolar lavage, nasopharyngeal aspirate, pleural fluid, sinus, sputum and tracheal aspirates;
- Diagnostic laboratory-based AST data with at least one of the following drugs used: amoxicillin-clavulanic acid, azithromycin, levofloxacin, cefixime, cefpodoxime and cefuroxime.

Exclusion criteria:

- Diagnostic labs with incomplete information regarding age, month of testing, and susceptibility status were excluded.
- Blood specimens from adults aged 18 years and older.

National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited diagnostic laboratories, which follow Clinical and Laboratory Standards Institute (CLSI) guidelines relevant over the 5-year period, were identified across India through an exhaustive pre-startup QC/assurance process as outlined:

- The process entailed identifying and approaching potential laboratories and hospitals located across India with a detailed questionnaire comprising 56 open- and closed-ended questions, which was validated by microbiology experts.
- The questionnaire responses were collected, reviewed and discussed for further queries from the laboratories and hospitals.
- The final collated output was reviewed by the microbiology experts and the eligible laboratories and hospitals were shortlisted for the study.
- The main purpose of conducting the pre-startup QC/assurance activity was to ascertain the eligibility of the laboratories and hospitals by evaluating their current processes and standards pertaining to laboratory tiers, accreditation, certification, microbiological and technical requirements for culture growth, fastidious organisms related to AST and Proficiency Testing (PT) procedures, QC, and Quality Assurance (QA), as well as the pre-examination and examination of isolates and guidelines, clinical correlation and reporting.
- Data was collected from the laboratories and hospitals that fulfilled the eligibility criteria.

Based on the eligibility criteria, four centres were selected, of which three had a pan-India presence, and one was located in North India. The demographics, specimens, isolated organisms and diagnostic AST records were collected from the selected centres.

Sample size estimation: Sample size estimation was based on feasibility and estimation approaches. The total available sample was divided according to the prevalence of each organism (*H. influenzae* and *S. pneumoniae*) (30%-70%) observed in the pre-startup QC/assurance activity and the Survey of Antibiotic Resistance (SOAR) study [13]. Precision was then estimated for the susceptibility of each shortlisted antibiotic based on the proportions of susceptibilities for *H. influenzae* and *S. pneumoniae* reported in the SOAR study (data from India, 2012-2014) [13].

A total of 1,351 AST records conducted using automated culture systems were evaluated for this study, including 608 *H. influenzae* and 743 *S. pneumoniae* records (45:55 ratio), which were reported according to the standard AST results as % Sensitive, % Intermediate and % Resistant.

STATISTICAL ANALYSIS

The study results are presented as mean±SD and median (range) for age and frequency and proportions for age groups, sex, states and zones. The frequency and respective proportions were calculated to compare the year-wise temporal trends of the susceptibility patterns, as well as the susceptibility patterns between the pre- and post-pandemic periods, age groups, states and zones. The Odds Ratios (ORs) and exact 95% Confidence Intervals (CIs) comparing the susceptibility patterns of amoxicillin-clavulanic acid with other antibiotics were reported for each isolate. Isolates with n <20 were not interpreted for any of the results, as it was difficult to draw significant inferences considering the low sample size (as per EU/EEA (EARS-Net) 2021) [17].

RESULTS

Descriptive characteristics: Overall, 1,351 diagnostic AST records were extracted, including isolates collected from patients aged 0.01 to 96 years (mean±SD: 52.7±20.8), with 812 (60.1%) records from males and 1,257 (93.0%) records from adults (≥18 years) [Table/Fig-1]. Levofloxacin was the most tested antibiotic across all age groups and in different zones. Over 50% of the records were from

Parameters	Total	Amoxicillin-clavulanic acid	Azithromycin	Levofloxacin	Cefixime	Cefpodoxime	Cefuroxime
N†	**1351**	**334**	**755**	**1292**	**609**	**130**	**144**
Age; Years							
Mean±SD	52.7±20.8	52.7±21.9	51.3±20.4	52.5±20.7	50.7±19.7	43.9±18.2	44.8±19.2
Median (IQR)	57 (31)	58 (34)	54 (32)	57 (31)	54 (32)	40 (29)	42 (29)
Range (min, max)	0.01, 96	1, 93	1, 95	0.01, 96	2, 90	2, 85	2, 85
Sex; n (%)							
Male	812 (60.1)	207 (62)	437 (57.9)	781 (60.4)	343 (56.3)	75 (57.7)	85 (59)
Female	539 (39.9)	127 (38)	318 (42.1)	511 (39.6)	266 (43.7)	55 (42.3)	59 (41)
Age groups; n (%)							
Children (<18 years)	94 (7.0)	25 (7.5)	44 (5.8)	90 (7.0)	29 (4.8)	8 (6.2)	10 (6.9)
Adults (≥18 years)	1257 (93.0)	309 (92.5)	711 (94.2)	1202 (93.0)	580 (95.2)	122 (93.8)	134 (93.1)
State and zone; n (%)							
State							
Maharashtra	731 (54.1)	21 (6.3)	496 (65.7)	704 (54.5)	455 (74.7)	0	2 (1.4)
New Delhi	177 (13.1)	143 (42.8)	68 (9)	157 (12.2)	0	0	9 (6.3)
Telangana	124 (9.2)	123 (36.8)	122 (16.2)	124 (9.6)	123 (20.2)	123 (94.6)	123 (85.4)
Tamil Nadu	62 (4.6)	24 (7.2)	40 (5.3)	58 (4.5)	22 (3.6)	0	0
Gujarat	49 (3.6)	1 (0.3)	5 (0.7)	49 (3.8)	0	0	0
Uttar Pradesh	45 (3.3)	2 (0.6)	3 (0.4)	44 (3.4)	0	0	1 (0.7)
Himachal Pradesh	37 (2.7)	10 (3)	13 (1.7)	31 (2.4)	1 (0.2)	0	0
Karnataka	29 (2.1)	4 (1.2)	4 (0.5)	29 (2.2)	4 (0.7)	4 (3.1)	4 (2.8)
Assam	26 (1.9)	0	0	26 (2)	0	0	0
Other states*	71 (5.3)	6 (1.8)	4 (0.5)	70 (5.4)	4 (0.7)	3 (2.3)	5 (3.5)
Zone							
North	292 (21.6)	158 (47.3)	84 (11.1)	265 (20.5)	1 (0.2)	0	11 (7.6)
South	227 (16.8)	154 (46.1)	170 (22.5)	222 (17.2)	153 (25.1)	130 (100)	131 (91)
East	38 (2.8)	0	0	38 (2.9)	0	0	0
West	785 (58.1)	22 (6.6)	501 (66.4)	758 (58.7)	455 (74.7)	0	2 (1.4)
Central	9 (0.7)	0	0	9 (0.7)	0	0	0
Year; n (%)							
2017	229 (17.0)	31 (9.3)	81 (10.7)	213 (16.5)	62 (10.2)	0	3 (2.1)
2018	244 (18.1)	49 (14.7)	120 (15.9)	232 (18.0)	90 (14.8)	12 (9.2)	17 (11.8)
2019	338 (25.0)	117 (35)	215 (28.5)	330 (25.5)	184 (30.2)	59 (45.4)	61 (42.4)
2020	239 (17.7)	94 (28.1)	182 (24.1)	220 (17.0)	153 (25.1)	40 (30.8)	43 (29.9)
2021	151 (11.2)	31 (9.3)	94 (12.5)	149 (11.5)	83 (13.6)	17 (13.1)	18 (12.5)
2022	150 (11.1)	12 (3.6)	63 (8.3)	148 (11.5)	37 (6.1)	2 (1.5)	2 (1.4)
Pre-pandemic (2017–2019)	811 (60.0)	197 (59.0)	416 (55.1)	775 (60.0)	336 (55.2)	71 (54.6)	81 (56.3)
Post-pandemic (2020–2022)	540 (40.0)	137 (41.0)	339 (44.9)	517 (40.0)	273 (44.8)	59 (45.4)	63 (43.8)

[Table/Fig-1]: Descriptive characteristics of AST records from January 2017 to July 2022 for *H. influenzae* and/or *S. pneumoniae*.
†Each isolate was tested for more than one antibiotic
*Other states include Andhra Pradesh, Bihar, Chhattisgarh, Goa, Haryana, Jammu and Kashmir, Kerala, Madhya Pradesh, Manipur, Punjab, Rajasthan, Uttarakhand, and West Bengal

the Western region {785 (58.1%)}, primarily from Maharashtra. Most records were from the year 2019 {338 (25%)}; whereas, 811 (60.0%) records were from the pre-pandemic period and 540 (40.0%) records were from the post-pandemic period.

Susceptibility patterns of *H. influenzae* and *S. pneumoniae* to antibiotics: Overall, there were 608 AST records of *H. influenzae* and 743 AST records of *S. pneumoniae*. Most *H. influenzae* {566/608 (93.1%)} and *S. pneumoniae* {554/743 (74.6%)} isolates were from sputum samples. Among the studied isolates, both organisms had high susceptibility to amoxicillin-clavulanic acid, i.e., 88.7% (n=86) against *H. influenzae* and 95.8% (n=227) against *S. pneumoniae* [Table/Fig-2].

Temporal trends of susceptibility patterns: For *H. influenzae*, susceptibility to amoxicillin-clavulanic acid remained nearly the same during 2019 {90% (n=27)} and 2020 {87.2% (n=41)}. Susceptibility to azithromycin decreased from 93.8% (n=61) in 2017 to 79.2% (n=42) in 2022. Susceptibility to levofloxacin remained consistent at 81.7% (n=49) in 2017 and 81.0% (n=51) in 2022. Susceptibility to cefixime decreased from 100% (n=61) in 2017 to 82.9% (n=29) in 2022 [Table/Fig-3]. For *S. pneumoniae*, susceptibility to amoxicillin-clavulanic acid remained high, ranging from 100% (n=23) in 2017 to 92.9% (n=26) in 2021, with some fluctuations over the years. For azithromycin, susceptibility remained nearly the same in 2019 {72.7% (n=48)} and 2020 {73.8% (n=31)} [Table/Fig-4].

Age group and zone-wise susceptibility patterns: For *H. influenzae* (n=608), there were 24 isolates from children (<18 years) and 584 from adults (≥18 years). Among children, the susceptibility of *H. influenzae* to azithromycin was 87.5% (n=21); however, the number of isolates for other antibiotics was <20, limiting clinical relevance [17]. Among adults, azithromycin {88.7% (n=486)} and amoxicillin-clavulanic acid {88.3% (n=83)} showed high susceptibility.

For *S. pneumoniae* (n=743), 70 isolates from children and 673 from adults were included in the analysis. Among children, the susceptibility of *S. pneumoniae* to amoxicillin-clavulanic acid

Specimen type	N (%)	Amoxicillin-clavulanic acid				Azithromycin				Levofloxacin				Cefixime				Cefpodoxime				Cefuroxime			
		N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)
H. influenzae (N=608)																									
N	**608**	**97**	**86 (88.7)**	**0**	**11 (11.3)**	**572**	**507 (88.6)**	**1 (0.2)**	**64 (11.2)**	**565**	**459 (81.2)**	**1 (0.2)**	**105 (18.6)**	**483**	**389 (80.5)**	**1 (0.2)**	**93 (19.3)**	**8**	**8 (100)**	**0**	**0**	**17**	**13 (76.5)**	**0**	**4 (23.5)**
Blood (children only)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Throat swab	12 (2.0)	2	1 (50.0)	0	1 (50.0)	9	7 (77.8)	0	2 (22.2)	11	10 (90.9)	0	1 (9.1)	9	7 (77.8)	0	2 (22.2)	0	0	0	0	0	0	0	0
Bronchoalveolar lavage	19 (3.1)	4	4 (100.0)	0	0	16	15 (93.8)	0	1 (6.2)	19	16 (84.2)	0	3 (15.8)	10	8 (80.0)	0	2 (20.0)	0	0	0	0	0	0	0	0
Nasopharyngeal aspirate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pleural fluid	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sinus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sputum	566 (93.1)	87	77 (88.5)	0	10 (11.5)	539	477 (88.5)	1 (0.2)	61 (11.3)	526	425 (80.8)	1 (0.2)	100 (19.0)	462	372 (80.5)	1 (0.2)	89 (19.3)	8	8 (100.0)	0	0	16	13 (81.2)	0	3 (18.8)
Tracheal aspirates	11 (1.8)	4	4 (100.0)	0	0	8	8 (100.0)	0	0	9	8 (88.9)	0	1 (11.1)	2	2 (100.0)	0	0	0	0	0	0	1	0	0	1 (100.0)
S. pneumoniae (N=743)																									
N	**743**	**237**	**227 (95.8)**	**0**	**10 (4.2)**	**183**	**133 (72.7)**	**0**	**50 (27.3)**	**727**	**535 (73.6)**	**20 (2.8)**	**172 (23.7)**	**126**	**115 (91.3)**	**0**	**11 (8.7)**	**122**	**119 (97.5)**	**0**	**3 (2.5)**	**127**	**111 (87.4)**	**0**	**16 (12.6)**
Blood (children only)	24 (3.2)	7	7 (100.0)	0	0	5	3 (60.0)	0	2 (40.0)	21	19 (90.5)	1 (4.8)	1 (4.8)	0	0	0	0	0	0	0	0	2	2 (100.0)	0	0
Throat swab	50 (6.7)	18	18 (100.0)	0	0	24	19 (79.2)	0	5 (20.8)	49	30 (61.2)	3 (6.1)	16 (32.7)	19	19 (100.0)	0	0	18	18 (100.0)	0	0	18	18 (100.0)	0	0
Bronchoalveolar lavage	57 (7.7)	11	11 (100.0)	0	0	7	7 (100.0)	0	0	54	34 (63.0)	4 (7.4)	16 (29.6)	4	4 (100.0)	0	0	4	4 (100.0)	0	0	4	3 (75.0)	0	1 (25.0)
Nasopharyngeal aspirate	1 (0.1)	0	0	0	0	0	0	0	0	1	1 (100.0)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pleural fluid	15 (2)	5	5 (100.0)	0	0	3	3 (100.0)	0	0	15	13 (86.7)	0	2 (13.3)	1	1 (100.0)	0	0	1	1 (100.0)	0	0	1	1 (100.0)	0	0
Sinus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sputum	554 (74.6)	176	166 (94.3)	0	10 (5.7)	137	99 (72.3)	0	38 (27.7)	545	404 (74.1)	11 (2.0)	130 (23.9)	102	91 (89.2)	0	11 (10.8)	99	96 (97.0)	0	3 (3.0)	101	86 (85.1)	0	15 (14.9)
Tracheal aspirates	42 (5.7)	20	20 (100.0)	0	0	7	2 (28.6)	0	5 (71.4)	42	34 (81.0)	1 (2.4)	7 (16.6)	0	0	0	0	0	0	0	0	1	1 (100.0)	0	0

[Table/Fig-2]: Susceptibility patterns of *H. influenza* and *S. pneumoniae* to antibiotics.
%S: Percentage sensitive; %I: Percentage intermediate; %R: Percentage resistant
*The number of isolates for antibiotics <20, had limited clinical relevance [17]

Year	Amoxicillin-clavulanic acid		Azithromycin		Levofloxacin		Cefixime	
	n (%)	N	n (%)	N	n (%)	N	n (%)	N
2017	-	-	61 (93.8)	65	49 (81.7)	60	61 (100.0)	61
2018	-	-	88 (90.7)	97	76 (85.4)	89	71 (91.0)	78
2019	27 (90.0)	30	137 (91.9)	149	126 (82.4)	153	120 (93.0)	129
2020	41 (87.2)	47	119 (85.0)	140	102 (78.5)	130	91 (79.1)	115
2021	-	-	60 (88.2)	68	55 (78.6)	70	17 (26.2)	65
2022	-	-	42 (79.2)	53	51 (81.0)	63	29 (82.9)	35

[Table/Fig-3]: Temporal trends of susceptibility patterns of *Haemophilus influenzae* to the antibiotics.
n: Number of isolates susceptible to the respective antibiotic; N: Total number of isolates tested for the respective antibiotic

Year	Amoxicillin-clavulanic acid		Azithromycin		Levofloxacin		Cefixime		Cefpodoxime		Cefuroxime	
	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N
2017	23 (100)	23	-	-	124 (81.0)	153	-	-	-		-	-
2018	40 (95.2)	42	17 (73.9)	23	104 (72.7)	143	-	-	-	-	-	-
2019	86 (98.9)	87	48 (72.7)	66	123 (69.5)	177	50 (90.9)	55	52 (98.1)	53	45 (84.9)	53
2020	42 (89.4)	47	31 (73.8)	42	64 (71.1)	90	36 (94.7)	38	37 (97.4)	38	32 (84.2)	38
2021	26 (92.9)	28	19 (73.1)	26	55 (69.6)	79	-	-	-	-	-	-
2022	-	-	-	-	65 (76.5)	85	-	-	-	-	-	-

[Table/Fig-4]: Temporal trends of susceptibility patterns of *Streptococcus pneumoniae* to the antibiotics.
n: Number of isolates susceptible to the respective antibiotic; NL: Total number of isolates tested for the respective antibiotic

was 100% (n=22). Among adults, cefpodoxime {97.4% (n=111)} and amoxicillin-clavulanic acid {95.4% (n=205)} showed high susceptibility. Age group and zone-wise susceptibility patterns are shown in [Table/Fig-5].

Susceptibility patterns before and after the COVID-19 pandemic: For *H. influenzae* (n=608), 327 (53.8%) isolates were from the pre-pandemic period, and 281 (46.2%) were from the post-pandemic period. The susceptibility of *H. influenzae* to amoxicillin-clavulanic acid remained nearly the same in the pre-pandemic (88.9%, n=40) and post-pandemic (88.5%, n=46) periods. Similarly, the susceptibility rates remained within a similar range in the pre- and post-pandemic periods for azithromycin (92.0%, n=286 and 84.7%, n=221) and levofloxacin (83.1%, n=251 and 79.1%, n=208). However, susceptibility to cefixime decreased from 94.0% (n=252) to 63.7% (n=137) from the pre- to post-pandemic period.

For *S. pneumoniae* (n=743), 484 (65.1%) and 259 (34.9%) isolates were from the pre-pandemic and post-pandemic periods, respectively. The susceptibility patterns of *S. pneumoniae* for each antibiotic remained similar during the pre- and post-pandemic periods: amoxicillin-clavulanic acid decreased from 98.0% (n=149) to 91.8% (n=78); azithromycin decreased from 73.3% (n=77) to 71.8% (n=56); levofloxacin decreased from 74.2% (n=351) to 72.4% (n=184); cefixime decreased from 92.6% (n=63) to 89.7% (n=52); cefpodoxime decreased from 98.5% (n=64) to 96.5% (n=55); and cefuroxime decreased from 88.6% (n=62) to 86.0% (n=49).

Trends for the susceptibility patterns before and after the COVID-19 pandemic are presented in [Table/Fig-6,7].

Susceptibility to amoxicillin-clavulanic acid versus susceptibility to other antibiotics: For *H. influenzae*, amoxicillin-clavulanic acid exhibited higher odds of susceptibility compared to levofloxacin (88.7% vs 81.2%, OR=1.80, 95% CI=0.92, 3.88) and cefixime (88.7% vs 80.5%, OR=1.89, 95% CI=0.95, 4.08), while amoxicillin-clavulanic acid and azithromycin showed similar odds of susceptibility (88.7% vs 88.6%, OR=1.00, 95% CI=0.50, 2.19). However, the CIs reported above include 1 for all comparisons, indicating that the ORs may not be statistically significant.

For *S. pneumoniae*, amoxicillin-clavulanic acid showed higher odds of susceptibility than azithromycin (95.8% vs 72.7%, OR=8.49, 95% CI=4.08, 19.44), levofloxacin (95.8% vs 73.6%, OR=8.13, 95% CI=4.22, 17.57), cefixime (95.8% vs 91.3%, OR=2.17, 95% CI=0.81, 5.87), and cefuroxime (95.8% vs 87.4%, OR=3.26, 95% CI=1.34, 8.32). While amoxicillin-clavulanic acid showed lower odds of susceptibility compared to cefpodoxime, this comparison may not be significant as the CI includes 1 (95.8% vs 97.5%, OR=0.57, 95% CI=0.10, 2.28).

Susceptibility to amoxicillin-clavulanic acid versus susceptibility to other antibiotics is presented in [Table/Fig-8,9].

DISCUSSION

S. pneumoniae and *H. influenzae* are common pathogens causing RTIs, and prompt antibiotic intervention is crucial for effective management. AMR significantly influences the selection of antibiotics for managing RTIs. In India, data on antibiotic susceptibility patterns are mostly sporadic, and there is a paucity of national AMR surveillance programs. A pan-India study examining community pathogens' susceptibility to commonly prescribed antibiotics for RTIs can provide a comprehensive understanding of antibiotic susceptibility trends in India.

Of the total 1,351 isolate records, majority (n=1,292) were tested for levofloxacin. This is likely due to a skewed testing pattern across laboratories, more prescriptions for testing levofloxacin susceptibility, or an increased prescription of this broad-spectrum antibiotic for RTIs. However, it is important to note that levofloxacin is classified as a 'Watch' antibiotic by the WHO AWaRe classification, indicating a higher potential for resistance [18]. Moreover, levofloxacin is a reserve drug used for multidrug-resistant or rifampicin-resistant tuberculosis [19], and its inappropriate use in patients with RTIs may reduce the therapeutic effect on tuberculosis [20]. Levofloxacin's effectiveness in treating RTIs is commendable, but its judicious prescription is crucial to prevent the emergence of resistance.

In this study, *H. influenzae* showed high susceptibility rates to amoxicillin-clavulanic acid (88.7%) and azithromycin (88.6%). Similar susceptibility patterns to amoxicillin-clavulanic acid were observed in the Survey of Antibiotic Resistance (SOAR) (97%) and Tigecycline Evaluation and Surveillance Trial (TEST) studies (89.1%) [13,21]. For azithromycin, susceptibility rates of 94.7% and 96.1% were reported in the SOAR study and a study by Keerthana S and Appalaraju MT [13,22]. Regarding *S. pneumoniae*, the current study reported a susceptibility of 95.8% to amoxicillin-clavulanic acid and 72.7% to azithromycin. The SOAR and TEST studies also revealed high susceptibility rates (97% in India and 88% in Asia, respectively) to amoxicillin-clavulanic acid, while azithromycin susceptibility was reported at 66.3% in SOAR but was much lower

Parameters	Overall	Amoxicillin-clavulanic acid				Azithromycin				Levofloxacin				Cefixime				Cefpodoxime				Cefuroxime			
		N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)	N	n (%S)	n (%I)	n (%R)
***H. influenzae* (N=608)**																									
N	**608**	**97**	**86 (88.7)**	**0**	**11 (11.3)**	**572**	**507 (88.6)**	**1 (0.2)**	**64 (11.2)**	**565**	**459 (81.2)**	**1 (0.2)**	**105 (18.6)**	**483**	**389 (80.5)**	**1 (0.2)**	**93 (19.3)**	**8**	**8 (100)**	**0**	**0**	**17**	**13 (76.5)**	**0**	**4 (23.5)**
Age groups (years)																									
Children (<18)	24	3	3 (100.0)	0	0	24	21 (87.5)	0	3 (12.5)	24	18 (75.0)	0	6 (25.0)	21	18 (85.7)	0	3 (14.3)	0	0	0	0	0	0	0	0
Adults (≥18)	584	94	83 (88.3)	0	11 (11.7)	548	486 (88.7)	1 (0.2)	61 (11.1)	541	441 (81.5)	1 (0.2)	99 (18.3)	462	371 (80.3)	1 (0.2)	90 (19.5)	8	8 (100.0)	0	0	17	13 (76.5)	0	4 (23.5)
Zone																									
North	59	49	44 (89.8)	0	5 (10.2)	47	47 (100.0)	0	0	45	41 (91.1)	0	4 (8.9)	1	1 (100.0)	0	0	0	0	0	0	6	4 (66.7)	0	2 (33.3)
South	36	29	26 (89.7)	0	3 (10.3)	32	28 (87.5)	0	4 (12.5)	33	26 (78.8)	0	7 (21.2)	28	23 (82.1)	0	5 (17.9)	8	8 (100.0)	0	0	9	7 (77.8)	0	2 (22.2)
East	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
West	512	19	16 (84.2)	0	3 (15.8)	493	432 (87.6)	1 (0.2)	60 (12.2)	486	391 (80.5)	1 (0.2)	94 (19.3)	454	365 (80.4)	1 (0.2)	88 (19.4)	0	0	0	0	2	2 (100.0)	0	0
Central	1	0	0	0	0	0	0	0	0	1	1 (100.0)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
***S. pneumoniae* (N=743)**																									
N	**743**	**237**	**227 (95.8)**	**0**	**10 (4.2)**	**183**	**133 (72.7)**	**0**	**50 (27.3)**	**727**	**535 (73.6)**	**20 (2.8)**	**172 (23.7)**	**126**	**115 (91.3)**	**0**	**11 (8.7)**	**122**	**119 (97.5)**	**0**	**3 (2.5)**	**127**	**111 (87.4)**	**0**	**16 (12.6)**
Age groups (years)																									
Children (<18)	70	22	22 (100.0)	0	0	20	12 (60.0)	0	8 (40.0)	66	52 (78.8)	2 (3.0)	12 (18.2)	8	8 (100.0)	0	0	8	8 (100.0)	0	0	10	9 (90.0)	0	1 (10.0)
Adults (≥18)	673	215	205 (95.4)	0	10 (4.6)	163	121 (74.2)	0	42 (25.8)	661	483 (73.1)	18 (2.7)	160 (24.2)	118	107 (90.7)	0	11 (9.3)	114	111 (97.4)	0	3 (2.6)	117	102 (87.2)	0	15 (12.8)
Zone																									
North	233	109	109 (100.0)	0	0	37	19 (51.4)	0	18 (48.7)	220	155 (70.5)	7 (3.2)	58 (26.4)	0	0	0	0	0	0	0	0	5	5 (100.0)	0	0
South	191	125	115 (92.0)	0	10 (8.0)	138	109 (79.0)	0	29 (21.0)	189	168 (88.9)	1 (0.5)	20 (10.6)	125	114 (91.2)	0	11 (8.8)	122	119 (97.5)	0	3 (2.5)	122	106 (86.9)	0	16 (13.1)
East	38	0	0	0	0	0	0	0	0	38	24 (63.2)	2 (5.3)	12 (31.6)	0	0	0	0	0	0	0	0	0	0	0	0
West	273	3	3 (100.0)	0	0	8	5 (62.5)	0	3 (37.5)	272	183 (67.3)	10 (3.7)	79 (29)	1	1 (100.0)	0	0	0	0	0	0	0	0	0	0
Central	8	0	0	0	0	0	0	0	0	8	5 (62.5)	0	3 (37.5)	0	0	0	0	0	0	0	0	0	0	0	0
Other States*	67	5	4 (80.0)	0	1 (20.0)	2	2 (100.0)	0	0	67	40 (59.7)	3 (4.5)	24 (35.8)	2	1 (50.0)	0	1 (50.0)	2	1 (50.0)	0	1 (50.0)	3	2 (66.7)	0	1 (33.3)

[Table/Fig-5]: Age group- and zone-wise susceptibility patterns of *Haemophilus influenzae* and *Streptococcus pneumoniae* to antibiotics.
%I: Percentage intermediate; %R: Percentage resistant; %S: Percentage sensitive
*The number of isolates for antibiotics <20, had limited clinical relevance [17]

Time period	Amoxicillin-clavulanic Acid		Azithromycin		Levofloxacin		Cefixime	
	n (%)	N	n (%)	N	n (%)	N	n (%)	N
Pre-pandemic (2017-2019) {327 (53.8%)}	40 (88.9%)	45	286 (92.0%)	311	251 (83.1%)	302	252 (94.0%)	268
Post-pandemic (2020-2022) {281 (46.2%)}	46 (88.5%)	52	221 (84.7%)	261	208 (79.1%)	263	137 (63.7%)	215

[Table/Fig-6]: Susceptibility patterns of *H. influenzae* to the antibiotics in pre-COVID-19 pandemic versus post-pandemic scenario.
n: Number of isolates susceptible to the respective antibiotic; N: Total number of isolates tested for the respective antibiotic

Time period	Amoxicillin-clavulanic acid		Azithromycin		Levofloxacin		Cefixime		Cefpodoxime		Cefuroxime	
	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N
Pre-pandemic (2017-2019) {484 (65.1%)}	149 (98.0%)	152	77 (73.3%)	105	351 (74.2%)	473	63 (92.6%)	68	64 (98.5%)	65	62 (88.6%)	70
Post-pandemic (2020-2022) {259 (34.9%)}	78 (91.8%)	85	56 (71.8%)	78	184 (72.4%)	254	52 (89.7%)	58	55 (96.5%)	57	49 (86.0%)	57

[Table/Fig-7]: Susceptibility patterns of *S. pneumoniae* to the antibiotics in pre-COVID-19 pandemic versus post-pandemic scenario.
n: Number of isolates susceptible to the respective antibiotic; N: Total number of isolates tested for the respective antibiotic

Antibiotics	Susceptible	Not susceptible*	% Susceptibility	OR (Exact 95% CI)
Amoxicillin-clavulanic acid (N=97)	86	11	**88.7%**	1.00 (0.50, 2.19)
Azithromycin (N=572)	507	65	**88.6%**	
Amoxicillin-clavulanic acid (N=97)	86	11	**88.7%**	1.80 (0.92, 3.88)
Levofloxacin (N=565)	459	106	**81.2%**	
Amoxicillin-clavulanic acid (N=97)	86	11	**88.7%**	1.89 (0.95, 4.08)
Cefixime (N=483)	389	94	**80.5%**	
Amoxicillin-clavulanic acid (N=97)	86	11	**88.7%**	NA#
Cefpodoxime (N=8)	8	0	**100.0%**	
Amoxicillin-clavulanic acid (N=97)	86	11	**88.7%**	2.38 (0.48, 9.74)
Cefuroxime (N=17)	13	4	**76.5%**	

[Table/Fig-8]: Susceptibility of amoxicillin-clavulanic acid versus susceptibility of all other antibiotics for *H. influenzae*.
*As per CLSI, 'Not susceptible' category includes isolates with 'Intermediate' and 'Resistant' susceptibility
OR: Odds ratio; CI: Confidence interval
#Since, we have 0 count in 'Not susceptible' category, hence OR cannot be computed

Antibiotics	Susceptible	Not susceptible*	% Susceptibility	OR (Exact 95% CI)
Amoxicillin-clavulanic acid (N=237)	227	10	**95.8%**	8.49 (4.08, 19.44)
Azithromycin (N=183)	133	50	**72.7%**	
Amoxicillin-clavulanic acid (N=237)	227	10	**95.8%**	8.13 (4.22, 17.57)
Levofloxacin (N=727)	535	192	**73.6%**	
Amoxicillin-clavulanic acid (N=237)	227	10	**95.8%**	2.17 (0.81, 5.87)
Cefixime (N=126)	115	11	**91.3%**	
Amoxicillin-clavulanic acid (N=237)	227	10	**95.8%**	0.57 (0.10, 2.28)
Cefpodoxime (N=122)	119	3	**97.5%**	
Amoxicillin-clavulanic acid (N=237)	227	10	**95.8%**	3.26 (1.34, 8.32)
Cefuroxime (N=127)	111	16	**87.4%**	

[Table/Fig-9]: Susceptibility of amoxicillin-clavulanic acid versus susceptibility of all other antibiotics for *S. pneumoniae*.
*As per CLSI, 'Not susceptible' category includes isolates with 'Intermediate' and 'Resistant' susceptibility
OR: Odds ratio; CI: Confidence interval

(32%) in TEST [13,21]. The current study focuses on the Indian population, unlike the SOAR and TEST studies, which considered a global population. Differences in susceptibility rates may be due to factors like antibiotic prescribing practices, the use of breakpoints like European Committee on Antimicrobial Susceptibility Testing (EUCAST) or CLSI standards, vaccination programs, geographical changes and age-related immune profiles.

The susceptibility of *H. influenzae* to levofloxacin observed in this study was 81.2%, comparable to the results of the SOAR study (85.2%); however, the susceptibility in the TEST study was 96.8% [21]. The susceptibility of *S. pneumoniae* to levofloxacin was 73.6% in the current study, similar to that reported by Sharma S et al., (79%), whereas it was higher in the TEST (97%) and SOAR (85.8%) studies [13,21,23].

In the current study, the susceptibility of *H. influenzae* to cefixime was 80.5%, while the number of isolates tested for cefpodoxime and cefuroxime was too low to draw any inference. The SOAR study reported high susceptibilities to cephalosporins (97% for cefixime and cefpodoxime and 99.3% for cefuroxime). For *S. pneumoniae*, the susceptibility to cefixime in the current study (91.3%) was considerably higher than that in the SOAR study (49.8%). Similarly, the present study showed higher susceptibilities to cefpodoxime (97.5%) and cefuroxime (87.4%) compared to the SOAR study (67.1% and 75.2%) [13].

The present study found high susceptibility of *H. influenzae* and *S. pneumoniae* to amoxicillin-clavulanic acid in India, indicating that penicillin resistance is not alarming, especially when combined with clavulanic acid. Furthermore, the susceptibility of *H. influenzae* and *S. pneumoniae* to common antibiotics remained high, with some variations between 2017 and 2022, except for a decrease in the susceptibility of *H. influenzae* to azithromycin and cefixime. Recently, limited Indian studies have evaluated the temporal trends of AMR in these organisms. However, susceptibility data in the Antimicrobial Testing Leadership and Surveillance (ATLAS) global database for India reported that *H. influenzae* isolates remained susceptible to amoxicillin-clavulanic acid and ceftriaxone from 2016 to 2019 [19]. The reduction in antibiotic susceptibility over time may be attributed to patients being exposed to various antibiotics through self-prescription and suboptimal dosages. The study found no significant temporal variation, emphasising the importance of adhering to proper antibiotic prescription guidelines to prevent misuse and reduce resistance.

Limitation(s)

There are several limitations to this retrospective study. Firstly, the required standards of laboratory chains and hospitals limited the number of laboratories that could participate, and the CLSI protocols of these laboratory chains and hospitals may differ between the participating centres. Additionally, the study's non randomised selection approach may not accurately represent the Indian population, which may also be due to a higher number of records being reported from the West. Furthermore, the isolates were not classified as invasive or non invasive. Considering that children have difficulty expectorating sputum, blood specimens were used for analysis, which may not accurately reflect RTIs.

Moreover, although different types of specimens were considered for inclusion, a few, such as sinus infection specimens, could not be included as these were not reported by the participating centres. Finally, the small number of isolates in many subgroups did not allow for definitive interpretation and the study lacked the statistical power to detect significance.

CONCLUSION(S)

In conclusion, both *H. influenzae* and *S. pneumoniae* showed high susceptibility rates to amoxicillin-clavulanic acid, followed by azithromycin. Bacteria showed higher susceptibility to second and third-generation cephalosporins than to azithromycin, and higher susceptibility to amoxicillin-clavulanic acid than to second-generation cephalosporins. The study underscores the need for continuous antibiotic susceptibility monitoring in the country and provides guidance for clinicians in making evidence-based decisions for managing RTIs.

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