Infection and Drug Resistance

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ORIGINAL RESEARCH

Shifts in Epidemiology and Antibiotic Resistance of Haemophilus Influenzae in Children From Chongqing (2019–2024): Pre-, During, and Post-COVID-19

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Objective: To comprehensively investigate the epidemiology and analyze the antimicrobial resistance of Haemophilus influenzae isolated from children in Chongqing before, during, and after the COVID-19 pandemic.

Methods: A total of 21,723 Haemophilus influenzae strains from four Chongqing hospitals during 2019–2024 were included. Antimicrobial susceptibility testing was conducted according to Clinical and Laboratory Standards Institute 2024 breakpoints using Kirby-Bauer method or automated systems. β-lactamase was detected by the cefinase disc method. Specimen types, age-and season-specific distributions, and antibiotic susceptibility results were analyzed.

Results: Among the isolates, 91.43% of infected children were under 6 years old and 57.30% were male. Sputum was the main source (94.22%). Detection rates were higher in spring and winter ($p < 0.001$). β-lactamase-positive strains accounted for 71.82% and BLNAR strains accounted for 4.99%. High resistance was found for ampicillin (79.05%), cefuroxime (58.95%), ampicillin-sulbactam (59.82%), sulfamethoxazole-trimethoprim (68.51%), azithromycin (49.67%), and cefixime (37.78%), while meropenem (0.48%), levofloxacin (0.11%), chloramphenicol (4.85%), ceftriaxone (0.62%), rifampicin (0.15%), tetracycline (5.55%), and cefepime (6.11%) showed low resistance. The COVID-19 pandemic affected resistance patterns: resistance to ampicillin, aztreonam, cefuroxime, amoxycillin-clavulanic, and ampicillin-sulbactam were higher before and after the COVID-19 pandemic than during it ($p< 0.001$). Throughout the pre-pandemic, pandemic, and post-pandemic periods, the resistance rates of sulfamethoxazole-trimethoprim cefixime and cefepime showed a downward trend, while the resistance rate of azithromycin showed an upward trend.

Conclusion: Haemophilus influenzae infections mainly occur in children under 6 years old, with seasonal peaks in spring and winter. The COVID-19 pandemic influenced infection patterns of specific age groups and resistance trends. Caution is required for commonly resistant antibiotics, and continuous resistance monitoring is necessary.

Keywords: haemophilus influenzae, children, antibiotics, antimicrobial resistance, COVID-19

Introduction

Haemophilus influenzae, a Gram-negative bacillus, is one of the most prevalent pathogenic bacteria responsible for community-acquired pneumonia. It commonly colonizes the nasopharynx of children and can trigger a diverse range of infectious diseases, such as otitis media, sinusitis, pneumonia, and meningitis.[1–5] Based on the presence of polysaccharide capsule antigen, Haemophilus influenzae strains are categorized into typeable and non-typeable Hi. The typeable strains are further classified into six serotypes (a to f), while non-capsulated strains are identified as nontypeable Haemophilus influenzae (NTHi).[6] Before effective Hib conjugate vaccines were implemented in the immunization programs, strains of Haemophilus influenzae type b (Hib) were the primary cause of bacterial meningitis among children.[7,8] Globally, as of 2022, 193 out of 194 World Health Organization member states had incorporated the Hib vaccine into their national immunization programs, a widespread adoption that has significantly reduced Hib-related

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diseases.[9] Consequently, in these regions, with the wide use of the Hib vaccine, NTHi has emerged as the principal cause of diseases caused by Haemophilus influenzae.[10] However, in China, the Hib vaccine is not part of the national immunization plan. Vaccination is voluntary and funded by families.[9] Due to factors such as public awareness, economic conditions, and local policies, coverage in China is likely lower and more uneven compared to countries with national programs. This may lead to differences in the epidemiology of Haemophilus influenzae in China (eg, serotype distribution and infection rates) from regions with high Hib vaccine usage. The appropriate use of antibiotics is essential for effective treatment, but the emergence of antimicrobial resistance poses a major challenge. In recent years, growing concerns have been raised about the increasing drug resistance rates in Haemophilus influenzae, which not only result in treatment failures but also contribute to elevated morbidity and mortality. Many reports indicate that the resistance rate of ampicillin and azithromycin in Haemophilus influenzae showed an increasing trend through the years, and there has been additional drug resistance to macrolides, fluoroquinolones and other beta-lactams such as carbapenems.[11–13]

Chongqing, situated in southwestern China and characterized by a subtropical humid climate with distinct four seasons and a cold, dry winter, is a major city with a large population and extensive population mobility, facilitated by a well-developed transportation network. These factors significantly influence the transmission dynamics of Haemophilus influenzae. However, during the COVID-19 pandemic, stringent public health measures were implemented across China, including lockdowns, social distancing, and enhanced hygiene protocols. These interventions effectively reduced the volume of population mobility in Chongqing and curbed the spread of COVID-19.[14,15] Concurrently, the epidemiological profiles of numerous pathogens, including Haemophilus influenzae, underwent substantial changes during this period.[16–19]

Notably, despite the potential impact of the COVID-19 pandemic on the epidemiology and drug resistance patterns of Haemophilus influenzae, there is a paucity of research investigating the comprehensive changes in these aspects among children before, during, and after the pandemic. As a city with high population mobility in the Sichuan-Chongqing region, Chongqing can serve as a representative example of urban areas under strict pandemic control in China. Our study aims to bridge this research gap by assessing the impact of the COVID-19 pandemic on the clinical epidemiology and drug resistance patterns of Haemophilus influenzae in children. The findings of this study will be instrumental in formulating targeted local treatment guidelines, curbing the misuse of antibiotics, and preventing the dissemination of drug-resistant strains, thereby contributing to the enhancement of local pediatric healthcare standards.

Materials and Methods

Research Object

This was a retrospective study was conducted in four hospitals in Chongqing in 2019 to 2024 (divided into three time segments: before the COVID-19 pandemic (2019), during the pandemic (2020–2022), and after the pandemic (2023–2024)). Data on age, sex, specimen type, and antibiotic susceptibility results were collected from laboratory records. To prevent bias caused by repeated isolates and ensure reproducibility, duplicate isolates were excluded using the following criteria: For each de-identified case, only the first isolate of a specific pathogen detected from any clinical specimen was included in the analysis. Subsequent isolates of the same pathogen from the same patient, regardless of specimen type or collection time, were excluded.

Antibiotics Susceptibility Testing and β-Lactamase Assay

The susceptibility testing was carried out by means of the Kirby-Bauer method or automated systems in accordance with the 2024 guideline of the Clinical and Laboratory Standards Institute (CLSI 2024). The antibiotics tested included ampicillin, aztreonam, meropenem, cefuroxime, levofloxacin, amoxycillin-clavulanic, ampicillin-sulbactam, chloramphenicol, ceftriaxone, sulfamethoxazole-trimethoprim, azithromycin, rifampicin, cefixime, tetracycline, cefepime. These antibiotics cover a wide range of antibacterial spectra and usage scenarios in local clinical practice, making them representative for evaluating the antimicrobial resistance of Haemophilus influenzae in this region. Haemophilus influenzae ATCC 49247 served as the quality control in the process. The detection of β-lactamase production was conducted with the cephalosporin thiophene paper (manufactured by Oxoid Company, UK). A red color change of the paper signified a positive result, indicating that the bacteria were capable of producing β-lactamase.

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Data Analysis and Statistics

The antimicrobial susceptibility data were analyzed with WHONET2024 software, and GraphPad Prism 9 software was employed to generate statistical graphs. The Pearson chi-squared test was used for statistical comparisons and performed with SPSS software (version 20.0). $P < 0.05$ was considered statistically significant.

Results

Population Characteristics

A total of 21,723 isolates of Haemophilus influenzae were collected from children: 4222 in 2019, 1431 in 2020, 4521 in 2021, 4048 in 2022, 3371 in 2023, 4130 in 2024. The isolates are mainly concentrated in young children, <1 year old accounting for 34.41%, 1–3 years old accounting for 39.16%, 4–6 years old accounting for 17.86%, 7–9 years old accounting for 5.24%, 10–12 years old accounting for 2.29%, and >12 years old accounting for 1.04%. In the analysis of gender, 57.30% of 21,723 participants were male (Table 1).

Among patients infected with Haemophilus influenzae, those under 1 year old were a high-risk group before the COVID-19 pandemic (in 2019), accounting for 46.14%. During the COVID-19 pandemic (in 2020–2022), children aged 1 to 3 years had a relatively higher proportion of infections, accounting for 41.92%. For individuals over 4 years old, the infection rate was relatively higher after the COVID-19 pandemic (in 2023–2024). ($p < 0.001$) (Figure 1).

Specimen Type and Seasonal Distribution

Among the 21,723 strains, the most common specimen type was sputum (94.22%), next is bronchoalveoar lavage fluid (3.18%), other specimen types including pus, secretions, blood, throat, nasopharynx swabs, vaginal swabs, eye secretions, ear secretions, urine, and other specimens, accounting for 2.60% (Table 2).

Analysis of detection status in different seasons, Haemophilus influenzae can be detected throughout the year. The detection rates of Haemophilus influenzae in spring (March to May), summer (June to August), and autumn (September to November) and winter (December to February) are as follows: 33.52%, 21.32%, 12.34%, and 32.82%. The detection rate is higher in spring and winter ($p<0.001$). In 2020, especially at the beginning of the year, due to the impact of the initial outbreak of the COVID-19 pandemic, the number of child patients was significantly lower (Figure 2).

The results of Antimicrobial Susceptibility Test

The resistance rates of 21,723 Haemophilus influenzae strains to ampicillin, aztreonam, meropenem, cefuroxime, levofloxacin, amoxycillin-clavulanic, ampicillin-sulbactam, chloramphenicol, ceftriaxone, sulfamethoxazole-trimethoprim,

Table 1 Characteristics of Population Studied

Characteristic	Total	Year, n (%)					
		2019	2020	2021	2022	2023	2024
Participants	21,723	4222	1431	4521	4048	3371	4130
Age group(years)							
<1	7475 (34.41)	1948 (46.14)	642 (44.86)	1599 (35.37)	1176 (29.05)	913 (27.08)	1197 (28.98)
1-3	8506 (39.16)	1662 (39.37)	577 (40.32)	1831 (40.50)	1784 (44.07)	1472 (43.67)	1180 (28.57)
4-6	3880 (17.86)	396 (9.38)	152 (10.62)	657 (14.53)	736 (18.18)	638 (18.93)	1301 (31.50)
7-9	1138 (5.24)	115 (2.72)	29 (2.03)	272 (6.02)	230 (5.68)	194 (5.75)	298 (7.22)
10-12	498 (2.29)	48 (1.14)	20 (1.40)	115 (2.54)	91 (2.25)	103 (3.06)	121 (2.93)
>12	226 (1.04)	53 (1.25)	11 (0.77)	47 (1.04)	31 (0.77)	51 (1.51)	33 (0.80)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Gender							
Male	12,448 (57.30)	2548 (60.35)	839 (58.63)	2522 (55.78)	2335 (57.68)	1892 (56.13)	2312 (55.98)
Female	9275 (42.70)	1674 (39.65)	592 (41.37)	1999 (44.22)	1713 (42.32)	1479 (43.87)	1818 (44.02)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

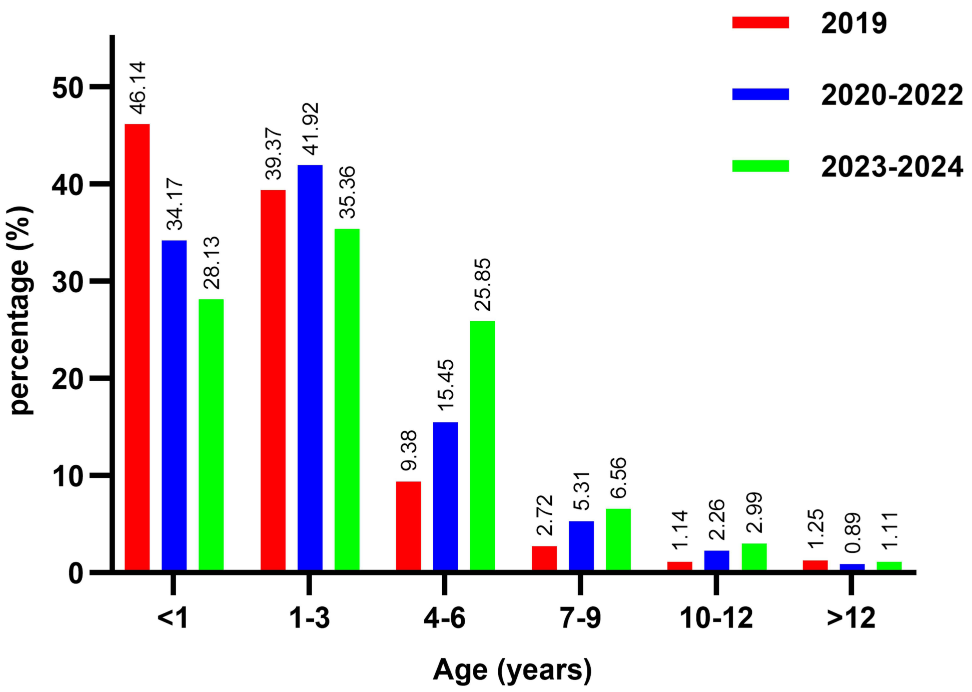

Figure 1 Age distribution in 2019 (before the COVID-19 pandemic), 2022–2022 (during the COVID-19 pandemic), and 2023–2024 (after the COVID-19 pandemic).

azithromycin, rifampicin, cefixime, tetracycline, cefepime were 79.05%, 21.61%, 0.48%, 58.95%, 0.11%, 16.90%, 59.82%, 4.85%, 0.62%, 68.51%, 49.67%, 0.15%, 37.78%, 5.55% and 6.11%, respectively (Figure 3). By analyzing the resistance trends of Haemophilus influenzae before, during, and after the COVID-19 pandemic, the results show that the resistance rates of ampicillin, aztreonam, cefuroxime, amoxycillin-clavulanic, and ampicillin-sulbactam were higher before and after the pandemic than during it ($p<0.001$). Throughout the pre-pandemic, pandemic, and post-pandemic periods, the resistance rates of sulfamethoxazole-trimethoprim cefixime and cefepime showed a downward trend, while the resistance rate of azithromycin showed an upward trend (Figure 4).

Among the 21,723 strains, 15,602 strains (71.82%) were β-lactamase-positive isolates, and 6121 strains (28.18%) were β-lactamase-negative isolates. The resistance rates to ampicillin, cefuroxime, ampicillin-sulbactam, chloramphenicol, sulfamethoxazole-trimethoprim, azithromycin, tetracycline and cefepime were significantly higher among β-lactamase-positive Haemophilus influenzae strains compared to β-lactamase-negative strains ($p<0.001$) (Figure 5). β-lactamase-negative and ampicillinresistant (BLNAR) isolates were present in 1084 strains (4.99%).

Table 2 Distribution of Specimen Types

Specimen Type	Total	Year, n (%)					
		2019	2020	2021	2022	2023	2024
	21,723	4222	1431	4521	4048	3371	4130
Sputum	20,467 (94.22)	3990 (94.50)	1342 (93.78)	4213 (93.19)	3776 (93.28)	3137 (93.06)	4009 (97.07)
Bronchoalveoar lavage fluid	691 (3.18)	145 (3.43)	77 (5.38)	157 (3.47)	114 (2.82)	95 (2.82)	103 (2.49)
Pus	50 (0.23)	7(0.17)	2(0.14)	13 (0.29)	110.27)	8(0.24)	9 (0.22)
Secretion	41 (0.19)	6(0.14)	4(0.28)	8(0.18)	15 (0.37)	3(0.09)	5 (0.12)
Blood	32 (0.15)	7(0.17)	4(0.28)	6(0.13)	4(0.10)	10 (0.29)	1 (0.03)
Other	442 (2.03)	67 (1.59)	2(0.14)	124 (2.74)	128 (3.16)	118 (3.50)	3 (0.07)

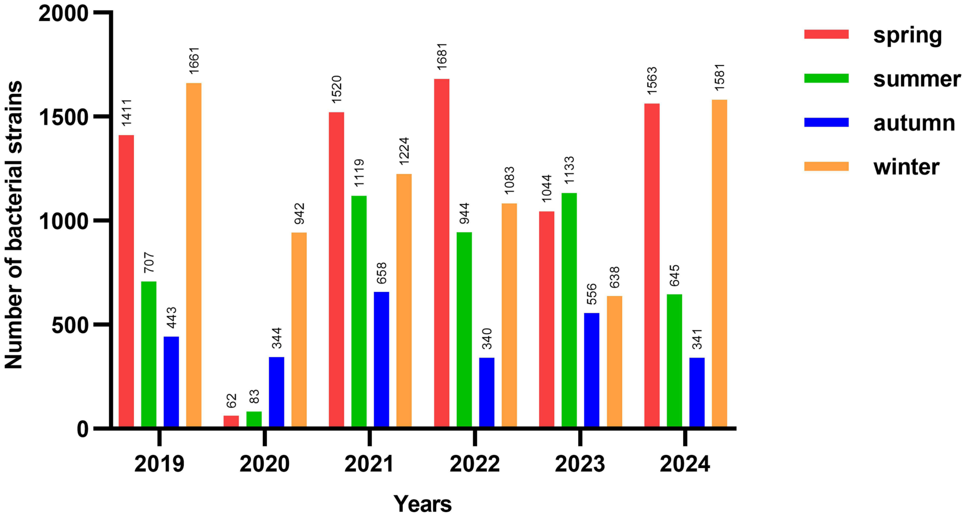

Figure 2 Seasonal distribution from 2019 to 2024.

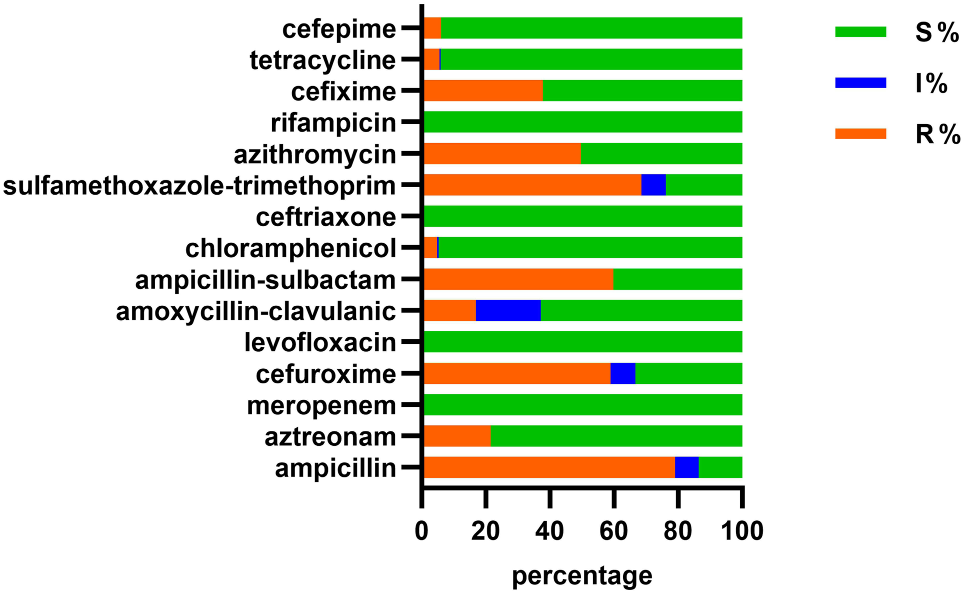

Figure 3 Antibiotic sensitivity patterns of Haemophilus influenzae strains from 2019 to 2024.

Discussion

Chongqing, as a major transportation hub and densely populated city in western China, experiences significant population mobility. The strict quarantine measures and non-pharmaceutical interventions (NPIs) such as social distancing implemented during the COVID-19 pandemic not only reshaped the public health landscape but also had a profound impact on the transmission dynamics of pathogens. Against this backdrop, it is crucial to explore how these measures have altered the epidemiological characteristics and resistance patterns of Haemophilus influenzae. This study, by analyzing data from 2019 to 2024, covering the pre-pandemic, pandemic, and post-pandemic periods, provides key insights into the dynamics of this bacterium in pediatric populations.

This study reveals significant dynamic changes in the epidemiological characteristics of Haemophilus influenzae among children. In terms of age distribution, children aged 6 years and below accounted for 91.43% of the infected cases, with infants and toddlers under 3 years old being particularly vulnerable, which is closely related to the immature immune system of this population. Notably, there were differences in age distribution during different stages of the

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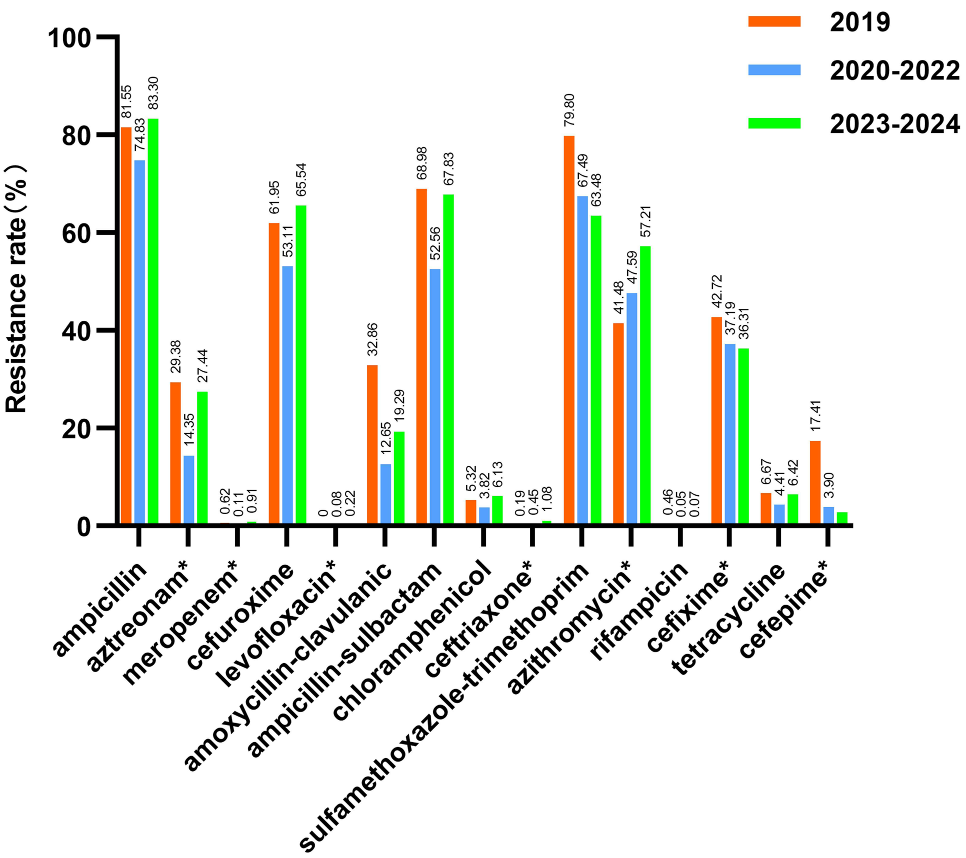

Figure 4 Analysis of antibiotic resistance rate of Haemophilus influenzae in 2019 (before the COVID-19 pandemic), 2022–2022 (during the COVID-19 pandemic), and 2023–2024 (after the COVID-19 pandemic) (*Rate of non-susceptible).

pandemic: In 2019, infants under 1 year old were at the highest risk due to their immature immune systems and close contact with family members; from 2020 to 2022, children aged 1–3 years became the main infected group because they had difficulty strictly adhering to NPIs, increasing their exposure risk; after 2023, with the relaxation of social restrictions, the infection rate among children over 4 years old increased. Additionally, Haemophilus influenzae infections exhibited a distinct seasonality, with the proportions in winter (32.82%) and spring (33.52%) being significantly higher than those in summer (21.32%) and autumn (12.34%), consistent with previous research findings.[4,20] However, The COVID-19 pandemic in early 2020 had a significant impact on the study. Stringent prevention and control measures, such as social distancing, lockdowns, and reduced healthcare utilization, led to a substantial decline in the sample size in 2020, particularly in spring.[21] These measures not only limited the spread of SARS-CoV-2 but also likely affected the transmission dynamics of Haemophilus influenzae.[22,23]

Analysis of drug resistance shows an upward trend in the resistance rates of Haemophilus influenzae to commonly used antibiotics. In this study, the resistance rate of pediatric strains in Chongqing to ampicillin reached 79.05%, and the positive rate of β-lactamase was 71.82%, indicating that β-lactamase production remains the main mechanism of resistance in this region.[24–26] Compared with national data, the resistance rate to ampicillin among children nationwide was 69.37% from 2017 to 2019, rising to 81.5% in 2023, confirming the increasing trend of resistance year by year and suggesting that ampicillin is no longer suitable for routine treatment.[11,13,27–29] Moreover, the resistance rates of the strains to cefuroxime (58.95%), ampicillin-sulbactam (59.82%), and azithromycin (49.67%) were all higher than the national levels from 2017 to 2019, while the resistance rates to ceftriaxone, meropenem, and other drugs were relatively low, making them alternative treatment options.

The results of this study show significant differences compared with other regions. For example, the proportion of BLNAR (β-lactamase-negative ampicillin-resistant) strains (4.99%) is higher than that in Sichuan (1.33%) but much

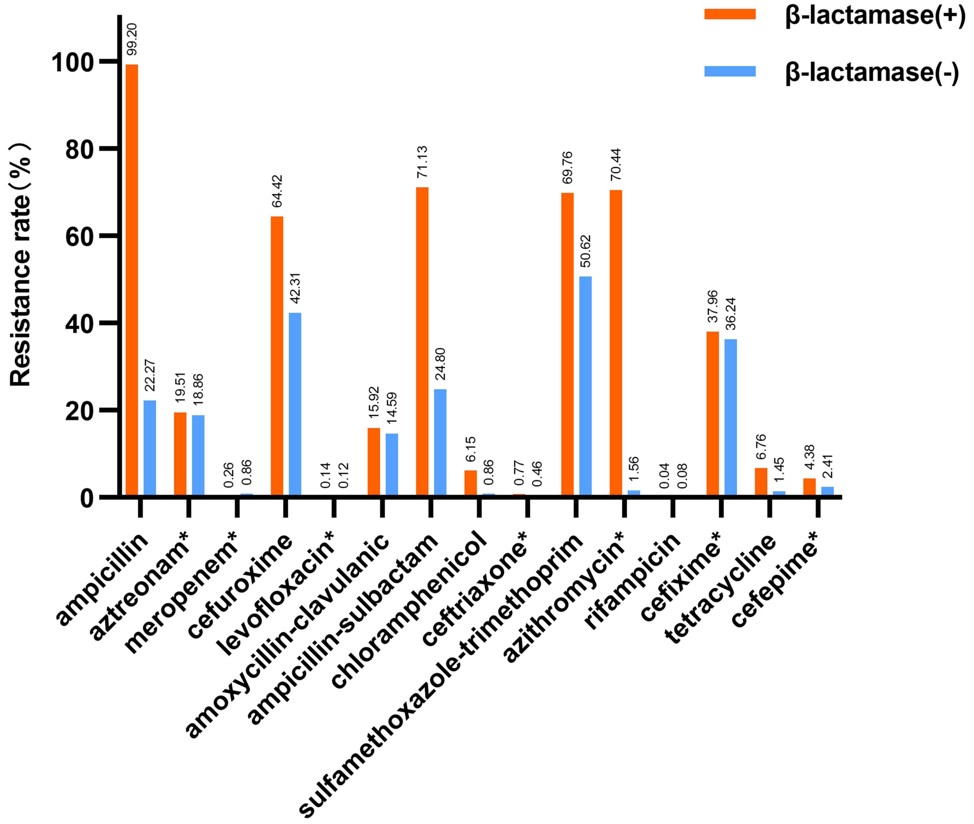

Figure 5 Comparison of antibiotic resistance of Haemophilus influenzae strains between β-lactamase positive and negative groups (*Rate of non-susceptible).

lower than that in regions such as Guangzhou (22.1%) and countries like Japan (60%).[30–34] The resistance may be due to mutations in the *ftsI* gene, which result in alterations in PBP3 and a decrease in the affinity for β-lactamase.[35,36] These differences may be attributed to variations in regional antibiotic use policies, population immunity levels, and the intensity of surveillance. For instance, differences in the prescription habits of β-lactam antibiotics across regions may lead to different exposure pressures on strains, thereby affecting the frequency of resistance gene mutations. Additionally, differences in population vaccination coverage (such as the Hib vaccine) and environmental transmission control measures may also alter the evolutionary trajectory of the strains.

Furthermore, the impact of the COVID-19 pandemic on resistance patterns showed unique characteristics in this study. During the pandemic, the resistance rates of Haemophilus influenzae to multiple antibiotics, including ampicillin, aztreonam, cefuroxime, amoxicillin-clavulanic acid, and ampicillin-sulbactam, decreased, possibly due to the diversion of medical resources, reduced patient consultations, and NPIs that limited bacterial transmission. However, the resistance rate to azithromycin increased continuously during the three stages, suggesting that changes in antibiotic use patterns during the pandemic (such as the empirical use of macrolide antibiotics for respiratory tract infections) may have accelerated the selection of resistant strains.

The results of this study have important guiding significance for clinical practice and public health strategies. Clinically, understanding regional resistance characteristics helps physicians select antibiotics precisely, reducing the risk of resistance caused by empirical medication and improving the treatment outcomes for pediatric infections. From a public health perspective, the findings provide a basis for formulating prevention and control strategies against the spread of drug-resistant strains, emphasizing the need to optimize antibiotic management and monitoring systems based on regional epidemiological characteristics.

However, this study has certain limitations. Firstly, as a retrospective study, the data may be subject to selection bias. Disruptions in healthcare services during the pandemic, including changes in patient triage and data recording priorities, may have affected the integrity and representativeness of the samples. Secondly, the study only included data from four hospitals in Chongqing, making it difficult to fully reflect the overall situation of the entire city or region. Finally, this study did not delve into the resistance mechanisms and genetic characteristics of the strains. Future research should combine molecular biology techniques to analyze resistance-related gene mutations and transmission patterns, providing theoretical support for precise prevention and control.

Conclusion

This study analyzed the antimicrobial resistance of Haemophilus influenzae in children in Chongqing during 2019–2024, covering pre-pandemic, pandemic, and post-pandemic periods. Key findings indicate that children under 6 years old are highly susceptible to Haemophilus influenzae infection, with spring and winter being peak seasons. The COVID-19 pandemic altered infection patterns among certain age groups and resistance profiles of antibiotics.

Our results highlight the necessity of continuous drug resistance surveillance, especially as healthcare systems recover post-pandemic, given the observed annual fluctuations in resistance rates. Rational antibiotic use and strict infection control measures remain essential; the pandemic experience demonstrated that public health interventions effectively curb pathogen spread, and similar strategies should be adopted to control drug-resistant Haemophilus influenzae. Notably, in the absence of explicit local guidelines for childhood Haemophilus influenzae infections, and considering the dynamic changes in antibiotic resistance observed in this study, we emphasize the critical need to promote pathogen-specific diagnosis (eg, through culture and susceptibility testing). This will facilitate the transition from empirical therapy to precise targeted treatment, ensuring that antibiotic selection is based on individual patient susceptibility data—ultimately safeguarding treatment efficacy and mitigating further resistance development.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent Waiver

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of Chongqing Red Cross Hospital (People's Hospital of Jiangbei District) (Approval Number: 2025CORCLL (X)-003). As this is a retrospective analysis using de-identified data obtained from routine microbiology laboratory tests, the Ethics Committee waived the requirement for informed consent. The data do not involve personal privacy (all identifiable information was excluded during collection) and pose no direct risk to participants, as the research does not involve intervention or individual patient identification.

Consent for Publication

All authors have thoroughly reviewed the manuscript and have provided their explicit consent for publication.

Author Contributions

All authors have made significant contributions to the reported research work, whether it is in the aspects of conceptualization, research design, data collection, or statistical analysis. They have participated in the drafting, revision, or rigorous review of the article; have given final approval to the version of the article to be published; have reached an agreement on the journal to which the article is submitted; and have agreed to be accountable for all aspects of this research work.

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Disclosure

The authors declare no conflicts of interest.

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