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Epidemiological Characteristics and Antimicrobial Resistance Profiles of Haemophilus influenzae Respiratory Infections in Hospitalized Children: A 7-Year Retrospective Study in Kunming

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Epidemiological Characteristics and Antimicrobial Resistance Profiles of Haemophilus influenzae Respiratory

Infections in Hospitalized Children: A 7-Year Retrospective Study in Kunming

Objective To analyze age, sex, temporal patterns, co-detected pathogens and sputum-culture antimicrobial resistance of *Haemophilus influenzae* (Hi) respiratory infections among hospitalized children in Kunming from 2019 to 2025, so as to provide evidence for local prevention, control and rational selection of antimicrobial agents. **Methods** This retrospective study included hospitalized children diagnosed with Hi respiratory tract infection. We stratified and summarized epidemiological characteristics, co-infecting pathogens and antimicrobial susceptibility results of sputum isolates according to age group, month, season and gender. **Results** A total of 11,217 cases were confirmed by sputum culture or PCR. Annual case numbers fluctuated and increased overall, reaching the lowest level in 2020 and the highest in 2024–2025, with obvious concentration in winter and spring. The proportion of preschool and school-aged children gradually increased, whereas that of infants declined significantly ($P<0.001$). Although boys were still predominant, the proportion of girls rose year by year. Common co-detected pathogens covered *Streptococcus pneumoniae*, respiratory syncytial virus, parainfluenza virus, rhinovirus, adenovirus and *Mycoplasma pneumoniae*, and co-detection patterns varied remarkably by year, season and age. Ampicillin, trimethoprim-sulfamethoxazole and cefaclor showed high resistance, while ceftriaxone, cefotaxime, rifampicin, meropenem and quinolones kept good activity. **Conclusions** Paediatric Hi respiratory infections present a winter-spring bimodal epidemic and an age shift toward older children. Third-generation cephalosporins are recommended as first-line empirical therapy. Continuous local surveillance and susceptibility data should guide clinical antibiotic use.

【Keywords】 Haemophilus influenzae; epidemiological characteristics; antibiotics; antimicrobial resistance； Seasonal

Introduction

Haemophilus influenzae (Hi) is a major bacterial cause of lower respiratory tract infections in children, manifesting as bronchitis and pneumonia and occasionally progressing to invasive diseases such as meningitis and sepsis, which pose substantial threats to pediatric health [1]. During the COVID-19 pandemic, public health interventions including mask wearing, social distancing, school closures, and home confinement markedly reshaped the epidemiological landscape of pediatric respiratory pathogens and led to pronounced fluctuations in Hi detection rates [2].Surveillance data from multiple regions of China demonstrate that after the adjustment of pandemic control policies, the number of Hi isolates in children rebounded rapidly, accompanied by shifts in antimicrobial resistance phenotypes [3].

The epidemiological characteristics, serotype distribution, and resistance genotypes of Hi vary considerably across geographic regions. National surveillance data cannot directly substitute for local monitoring, and long-term continuous regional surveillance is critical for guiding rational clinical antimicrobial use [4–8]. Currently, large-sample Hi surveillance data covering the full pre-pandemic, pandemic containment, and post-adjustment periods remain scarce in Kunming. This study retrospectively collected clinical and laboratory data of hospitalized children with positive Hi etiology for respiratory tract infections at Kunming Children's Hospital from 2019 to 2025. We analyzed the annual, seasonal, age, and sex

distribution patterns, pathogen co-detection features, and sputum isolate susceptibility profiles, to provide evidence for local Hi infection control and standardized antimicrobial stewardship.

Materials and Methods

Study Population and Grouping

Hospitalized children with clinically diagnosed Hi-associated lower respiratory tract infections (Hi-LRTIs) at Kunming Children's Hospital between January 1, 2019 and December 31, 2025 were enrolled. Diagnosis of lower respiratory tract infection was established comprehensively based on chest imaging, clinical symptoms, and physical signs, in accordance with the Chinese Expert Consensus on Etiological Diagnosis and Clinical Management of Acute Respiratory Tract Infections in Children [1].

Positive Hi etiology was defined as recovery of Hi from qualified sputum specimens, or a positive real-time quantitative PCR result for Hi in sputum samples, combined with consistent clinical and radiographic findings. Qualified sputum specimens met the following criteria: squamous epithelial cells <10 per low-power field and leukocytes >25 per low-power field. For infants, criteria were moderately relaxed: squamous epithelial cells 10–25 per low-power field, with a leukocyte-to-squamous epithelial cell ratio >2.5. Unqualified specimens were excluded. When the same strain was repeatedly isolated from the same child during a single hospitalization, only the first isolate was included.

A total of 11,217 Hi-positive children (culture- or PCR-positive) were included for analyses of annual, seasonal, age, and sex distribution and pathogen co-detection. Antimicrobial susceptibility testing was performed on 2,503 non-duplicate Hi strains successfully isolated from qualified sputum specimens with complete susceptibility testing.

Pathogen co-detection was defined as concurrent detection of other bacterial, viral, or mycoplasmal pathogens in the same Hi-positive respiratory specimen. Age strata were: infant group (<1 year), toddler group (1 to <3 years), preschool group (3 to <6 years), and school-age group (≥6 years). Seasons were defined as spring (March–May), summer (June–August), autumn (September–November), and winter (December, January, February). All analyses were stratified by month, season, and sex.

Instruments and Detection Methods

Bacterial identification and antimicrobial susceptibility testing were performed using the VITEK 2 Compact automated microbiology system (bioMérieux, France). Equivocal results were confirmed by Kirby–Bauer disk diffusion and E-test. Susceptibility interpretation was uniformly based on Clinical and Laboratory Standards Institute (CLSI) M100 32nd edition (2022) breakpoints. To ensure comparability across the 7-year study period, all isolates were re-interpreted retrospectively using the 2022 breakpoints. Haemophilus influenzae ATCC 49247 served as the quality-control strain. Nucleic acid detection for viruses and M. pneumoniae was performed on the Applied Biosystems 7500 real-time quantitative PCR system (USA). All co-pathogen testing was conducted using the same respiratory specimens as those used for Hi detection.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software. Categorical variables are presented as counts and proportions (%). Between-group comparisons of proportions were conducted using the χ^2 test. When the overall test yielded $P<0.05$, pairwise comparisons were performed with Bonferroni correction. The Cochran–Armitage trend χ^2 test was applied to assess annual trends in age-group proportions and female case proportion. A two-sided P-value <0.05 was considered statistically significant.

Ethical Statement

This study was approved by the Ethics Committee of Kunming Children's Hospital (approval No. KCH-2026-012). As a retrospective laboratory-based surveillance study, the requirement for informed consent was waived by the ethics committee.

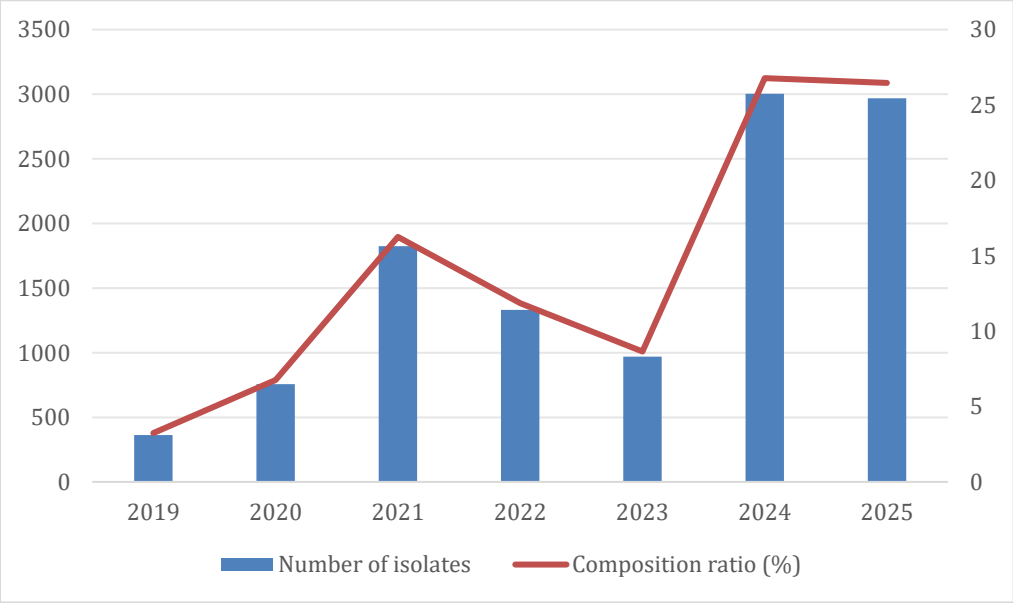
Results

Overall and Annual Distribution

A total of 11,217 hospitalized children with Hi-positive respiratory tract infections were enrolled over the 7-year period. In 2019, 363 cases (3.24%) were detected, representing an overall low baseline level. The number rose markedly to 757 cases (6.75%) in 2020, reached the first peak of 1,824 cases (16.26%) in 2021, then declined to 1,330 cases (11.86%) in 2022 and further to 970 cases (8.65%) in 2023—the lowest point after 2020. In 2024, cases rebounded sharply to 3,004 (26.78%), the 7-year peak, and remained at a similarly high level in 2025 with 2,969 cases (26.47%). The 2024–2025 total of 5,973 cases accounted for 53.25% of all cases, indicating that Hi detection in hospitalized children at our center entered a high-plateau phase after 2024.

Phased analysis showed 363 cases (3.24%) in the pre-pandemic year 2019. During the pandemic period (2020–2023), 4,881 cumulative cases (43.51%) were recorded, following a rise-peak-decline trajectory. In the post-adjustment period (2024–2025), 5,973 cumulative cases (53.25%) were detected—exceeding the 4-year pandemic total within two years and sustaining high levels consecutively. The mean annual detection was approximately 1,602 cases. The overall three-phase pattern—"low baseline – fluctuation – rebound to high plateau"—indicates that Hi detection in hospitalized children at our center has entered a new period of high activity in the post-pandemic era（Figure 1）.

Figure 1： Distribution of HI for each year from 2019 to 2025



Age Distribution and Shift Toward Older Age Groups

Across the full study period, there were 3,163 cases (28.20%) in the preschool group, 2,868 (25.57%) in the school-age group, 2,638 (23.51%) in the toddler group, and 2,548 (22.72%) in the infant group. The preschool and school-age groups together accounted for 53.77% of cases.

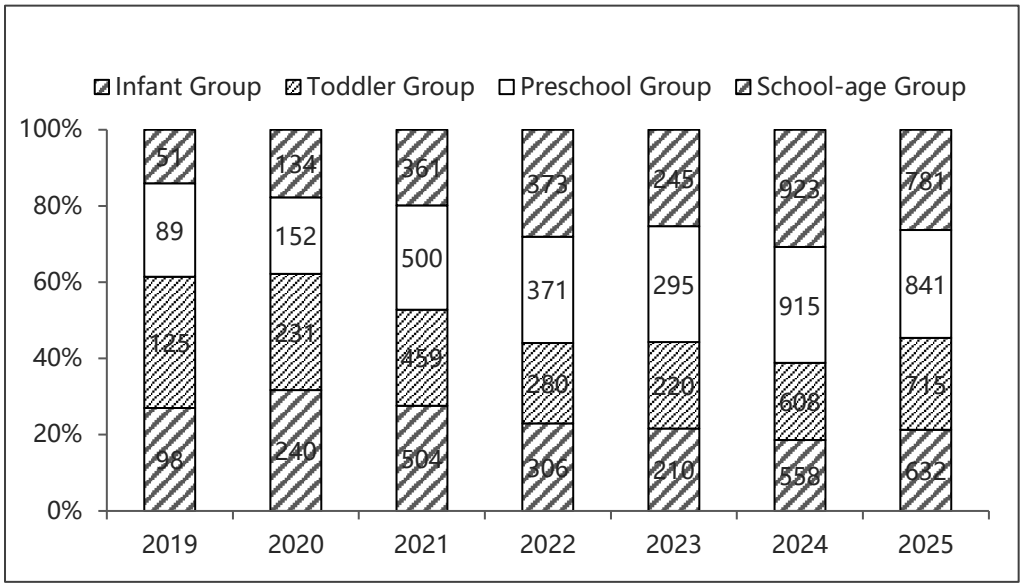
Infant cases peaked at 504 in 2021, fell to 210 in 2023, then rebounded to 558 and 632 in 2024 and 2025, respectively. Toddler cases peaked at 459 in 2021, dropped to 220 in 2023,

and rose to 608 and 715 in 2024 and 2025. Preschool cases grew continuously from 89 in 2019 to a peak of 915 in 2024, then declined slightly to 841 in 2025. School-age cases increased rapidly from 51 in 2019 to 923 in 2024 and 781 in 2025.

In terms of proportional shifts, the infant group proportion fell from 27.0% in 2019 to 18.6% in 2024, then rebounded to 21.3% in 2025. The toddler group proportion declined from 34.4% to 20.2% in 2024—the most pronounced drop—and rose to 24.1% in 2025. The preschool group proportion rose from 24.5% to 30.5% in 2024 (28.3% in 2025). The school-age group proportion increased from 14.0% to 30.7% in 2024, representing the primary driver of the age-structure shift.

The combined proportion of preschool and school-age groups rose from 38.6% in 2019 to 61.2% in 2024, and fell to 54.6% in 2025—but remained significantly higher than baseline. The Cochran–Armitage trend test confirmed a significant upward trend in this combined proportion over time ($P<0.001$). In 2024, for the first time in 7 years, annual case numbers in the school-age (923) and preschool (915) groups both exceeded those in the infant (558) and toddler (608) groups. These findings indicate an age shift toward older children among Hi-positive cases at our center, although the burden of Hi infection in young infants remains clinically important（Figure 2）.

Figure 2： Number and Percentage of Annual Haemophilus influenzae Cases by Age Group, 2019-2025



Monthly and Seasonal Distribution

December was the month with the highest detection over the 7 years (1,385 cases), while September had the lowest (564 cases). Months with >1,000 cases were December (1,385), November (1,085), and March (1,035), collectively accounting for 3,505 cases (31.25% of all cases). In 2024, peaks occurred in December, April, March, February, and January; in 2025, peaks clustered in January, February, November, October, and December, showing prominent winter seasonality（Figure 3）.

Year-by-year seasonal analysis showed winter was the highest-incidence season in 2019, 2023, 2024, and 2025, while spring was the peak in 2020 and 2021. Summer and autumn proportions remained relatively stable across years with minor fluctuations.

Winter and spring together accounted for 6,356 cases (56.67% of the total), while summer and autumn accounted for 4,861 cases (43.33%). Overall, Hi detection exhibited a winter–spring bimodal epidemic pattern, with winter as the dominant transmission period and spring as a secondary peak in Kunming（Figure 4）.

Figure 3： Number of Haemophilus influenzae cases per month from 2019 to 2025 (cases)

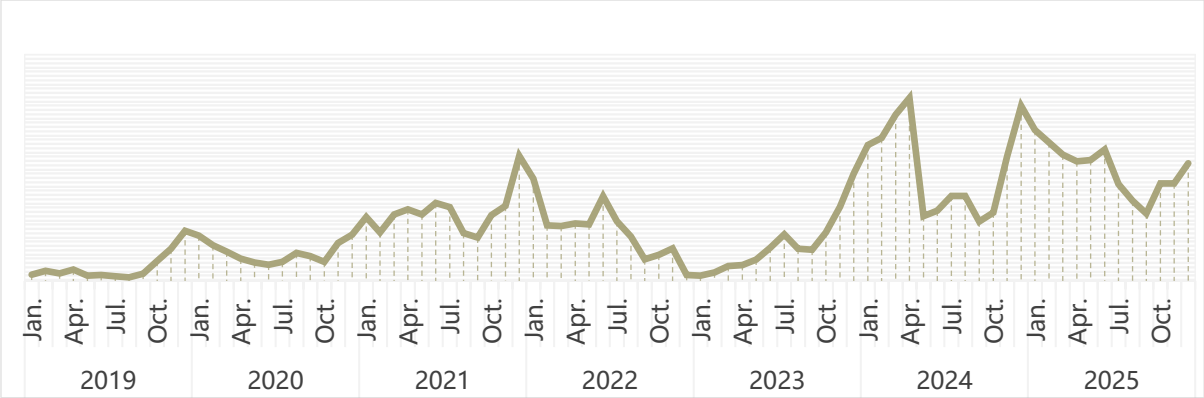
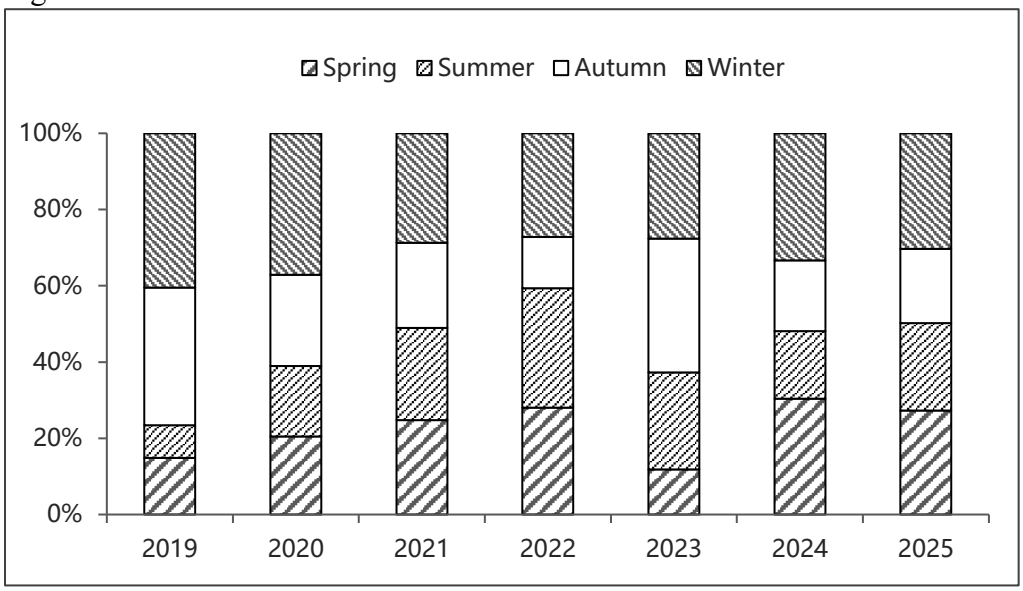


Figure 4： Seasonal Prevalence of Hi-LRTIs from 2019 to 2025



Sex Distribution and Trend in Female Proportion

Among all 11,217 children, 6,485 (57.81%) were male and 4,732 (42.19%) were female, yielding a male-to-female ratio of 1.38:1. Year-by-year male-to-female ratios were 1.63:1 (2019), 1.57:1 (2020), 1.53:1 (2021), 1.42:1 (2022), 1.31:1 (2023), 1.35:1 (2024), and 1.23:1 (2025).

The proportion of female cases showed a fluctuating upward trend overall, increasing by 6.8 percentage points from 2019 to 2025. Males outnumbered females in every year, but the

sex gap narrowed progressively. The Cochran–Armitage trend test confirmed a significant increase in female proportion over the study period ($P<0.01$).

Pathogen Co-detection Profiles

Among the 11,217 Hi-positive specimens, the top six co-detected pathogens were S. pneumoniae (2,732 cases), respiratory syncytial virus (2,034 cases), parainfluenza virus (2,024 cases), rhinovirus (1,848 cases), adenovirus (1,515 cases), and M. pneumoniae (1,282 cases).

Annually, co-detection counts of most pathogens were substantially higher in 2024–2025 than in earlier years. S. pneumoniae co-detection peaked in 2021 with a secondary peak in 2025; respiratory syncytial virus, parainfluenza virus, rhinovirus, and adenovirus all peaked during 2024–2025; M. pneumoniae co-detection reached its maximum in 2024. Seasonally, multiple pathogens showed high co-detection burdens in winter. Respiratory syncytial virus was most frequently detected in autumn, while rhinovirus and S. pneumoniae were more common in spring.

By age, preschool-aged children had the highest overall co-detection counts. Infants predominantly showed co-detection of respiratory syncytial virus and parainfluenza virus, while school-aged children had a relatively higher proportion of M. pneumoniae co-detection. Cumulative detections of these six major co-pathogens totaled 11,435 episodes, exceeding the total number of Hi cases (11,217), indicating that simultaneous detection of multiple pathogens per specimen is common in our center and that mixed co-detection is a widespread phenomenon. S. pneumoniae was the most frequently co-detected bacterium, and respiratory syncytial virus was the most frequently co-detected virus.

Importantly, pathogen counts were tallied independently; children positive for multiple pathogens were counted repeatedly for each pathogen. Therefore, these data reflect the co-detection epidemiology of each pathogen with Hi rather than the definitive prevalence of multiple infections（Table 1）.

Table 1: HI-L detection situation from 2019 to 2025

Category	Subcategory	Streptococcus	RSV	Parainfluenza virus	Rhinovirus	Adenovirus	Mycoplasma pneumoniae
Year	2019	72	78	73	8	49	20
Year	2020	240	102	130	41	62	100
Year	2021	706	145	228	42	119	296
Year	2022	368	198	316	47	257	263
Year	2023	143	337	349	172	328	126
Year	2024	505	580	385	681	347	327
Year	2025	698	594	537	857	353	150
Season	Spring	786	278	557	609	358	285

Season	Summer	761	279	419	442	366	250
Season	Autumn	568	808	364	461	228	272
Season	Winter	617	669	684	336	563	475
Age group	Infant	568	697	633	367	248	133
Age group	Toddler	706	640	529	372	407	277
Age group	Preschool	1006	558	674	782	636	507
Age group	School-age	452	139	188	327	224	365

Antimicrobial Resistance Analysis

Susceptibility testing was performed on 2,503 Hi strains isolated from qualified sputum specimens. High-level resistance (resistance rate >60%) was observed for ampicillin (80.33%), ampicillin–sulbactam (76.92%), trimethoprim-sulfamethoxazole (68.53%), and cefaclor (64.99%). Moderate resistance (20%–60%) was observed for cefuroxime (41.93%) and amoxicillin–clavulanate (27.73%). Low-level resistance (<10%) was observed for tetracycline (5.45%), chloramphenicol (5.34%), moxifloxacin (0.56%), ofloxacin (0.44%), cefotaxime (0.16%), and rifampicin (0.08%). No resistant strains were detected for ciprofloxacin, meropenem, cefepime, ceftriaxone, ceftazidime, or levofloxacin. The azithromycin resistance rate was 22.22%, but only 18 strains were evaluable, limiting representativeness; this result should not be used to infer local macrolide resistance. The overall β-lactamase positivity rate was 82.61%.

By antimicrobial class, β-lactam resistance was the dominant feature of local Hi strains. Penicillins and oral cephalosporins (ampicillin, ampicillin–sulbactam, cefaclor) showed universally high resistance, as did trimethoprim-sulfamethoxazole. In contrast, third-generation cephalosporins (ceftriaxone, cefotaxime), carbapenems (meropenem), and quinolones (levofloxacin, ciprofloxacin, moxifloxacin, ofloxacin) maintained high susceptibility, representing low-resistance therapeutic options. The 82.61% β-lactamase positivity rate aligns with the high ampicillin resistance rate, indicating that β-lactamase production is a key resistance mechanism in local Hi strains(Table 2).

Table 2: Drug susceptibility test results of 503 Haemophilus influenzae strains from sputum cultures

Antimicrobial agent	Susceptible	Intermediate	Resistant	Resistance rate (%)

Ampicillin	378	101	1956	80.33
Trimethoprim-sulfamethoxazole	699	82	1701	68.53
Cefaclor	793	63	1589	64.99
Cefuroxime	1303	122	1029	41.93
Amoxicillin/clavulanate	1786	7	688	27.73
Tetracycline	2297	47	135	5.45
Chloramphenicol	2329	13	132	5.34
Ampicillin/sulbactam	9	0	30	76.92
尾-lactamase	4	0	19	82.61
Moxifloxacin	1938	0	11	0.56
Ofloxacin	2471	0	11	0.44
Azithromycin	14	0	4	22.22
Cefotaxime	2434	0	4	0.16
Rifampicin	2473	8	2	0.08
Cephalothin	2	0	1	33.33
Ciprofloxacin	34	0	0	0
Meropenem	43	0	0	0
Cefepime	18	0	0	0
Ceftriaxone	43	0	0	0
Ceftazidime	43	0	0	0
Levofloxacin	33	0	0	0

Discussion

Annual and Seasonal Epidemiological Characteristics

The present results show that the number of Hi-positive detections remained low in the early pandemic containment phase, peaked once in 2021, declined during 2022–2023, then rebounded sharply in 2024 and persisted at high levels through 2025. This trajectory is broadly consistent with reports from Chongqing, Shandong, and Henan provinces [2,3,4,8]. The pattern is likely explained by reduced respiratory pathogen transmission during the pandemic due to mask wearing, social distancing, and reduced gatherings, which lowered Hi detection. Following the lifting of public health restrictions, children returned to school and resumed group activities, re-establishing transmission chains and driving a marked rebound in cases [8,9]. Additionally, improved laboratory capacity and increased clinician awareness of specimen submission may have contributed to higher detection rates in recent years.

Seasonally, Hi detection in Kunming followed a winter-dominant, spring-secondary bimodal pattern, similar to findings from southern Chinese cities such as Chongqing and Guangzhou [4,5]. However, seasonal patterns vary markedly across China, with some regions reporting a single spring peak or spring–summer predominance, reflecting geographic heterogeneity in Hi epidemiology [6,7].

Low winter–spring temperatures impair respiratory mucosal defenses, and increased indoor crowding facilitates Hi transmission. Concurrently, winter and spring are peak seasons for respiratory infections in Kunming, with higher visit volumes and specimen submission rates, which also inflate detection counts. The observed peaks therefore reflect the combined effects of pathogen transmissibility, healthcare-seeking behavior, and testing practices.

Age Distribution and the Shift Toward Older Age Groups

We observed a progressive age shift toward older children, with rising proportions of preschool and school-aged cases and a declining infant proportion—a trend also documented in surveillance studies from Chongqing and Wuhan [4,6].

Several mechanisms may underlie this shift. Following widespread Hib conjugate vaccine rollout, Hib-associated invasive infections in young infants have declined dramatically, and nontypeable H. influenzae (NTHi)—which more commonly colonizes and infects older children—has become the dominant strain [10,11]. Additionally, post-pandemic reopening has substantially increased group exposure among preschool and school-aged children [12].

Several limitations must be acknowledged. This study included only hospitalized children with submitted specimens. Older children are better able to cooperate with sputum collection, and clinicians have increasingly ordered multiplex pathogen testing for older age groups over time. The observed age shift therefore reflects the composition of tested cases and cannot be directly extrapolated to population-level incidence trends. Furthermore, despite the declining proportion, infants remain at highest risk for invasive Hi disease, and clinical vigilance for Hi infection in this age group is essential [13].

Sex Distribution Characteristics

Males accounted for 57.81% of cases, outnumbering females, while the female proportion increased gradually year by year and the male–female gap narrowed. There is no established evidence of inherent sex-based differences in Hi susceptibility; changes in sex composition are more likely attributable to healthcare-seeking patterns, family medical behavior, and differential exposure opportunities between boys and girls across age groups. Sex alone should not be used as a risk predictor for Hi infection.

Characteristics of Pathogen Co-detection

Hi is frequently co-detected with S. pneumoniae and respiratory viruses [1,20]. The co-detected pathogen spectrum in this study was dominated by S. pneumoniae, respiratory syncytial virus, parainfluenza virus, rhinovirus, adenovirus, and M. pneumoniae. The

synchronous rise in co-pathogen detection during 2024–2025 mirrors the overall Hi case rebound.

This increase likely stems from two factors. First, co-circulation of multiple respiratory pathogens following pandemic reopening increased mixed exposure. Second, the widespread adoption of multiplex nucleic acid testing and broader testing indications have improved detection of co-pathogens [9].

Seasonally, winter carries the highest co-detection burden. Age-stratified patterns align with established epidemiology: preschool-aged children bear the highest overall co-detection burden; infants predominantly co-carry respiratory syncytial virus and parainfluenza virus; school-aged children more frequently show M. pneumoniae co-detection. Clinical interpretation of Hi-positive results should consider the contemporary local pathogen background and the child's age, rather than relying on a single positive test in isolation.

As noted above, pathogen counts were tallied per organism rather than per patient, so the true prevalence of multiple infections could not be precisely estimated—an important limitation of this study.

Antimicrobial Resistance Characteristics

β-lactam resistance is the most prominent antimicrobial resistance phenotype in Hi, mediated primarily by β-lactamase production and PBP3 gene mutations, which confer resistance to ampicillin and selected oral cephalosporins [14]. Local isolates showed 80.33% ampicillin resistance and 82.61% β-lactamase positivity, with similarly elevated resistance to cefaclor and cefuroxime—consistent with findings from other Chinese regions [4,14].Third-generation cephalosporins and carbapenems retained high in vitro susceptibility, making them appropriate for moderate-to-severe drug-resistant Hi infections [18,19]. The trimethoprim-sulfamethoxazole resistance rate (68.53%) was lower than the 84.28% reported in some southwestern regions, further confirming substantial regional variation in resistance profiles [15,16].Rifampicin and quinolones have very low resistance rates, but safety considerations preclude their routine use in children. The azithromycin resistance estimate was based on only 18 evaluable strains, which is too small to support conclusions about local macrolide resistance. Although increasing azithromycin resistance in Hi—linked to M. pneumoniae epidemics and rising macrolide consumption—has been reported in multiple Chinese regions [6,14], our data are insufficient to validate this trend.Third-generation cephalosporins showed excellent overall susceptibility, but they are parenteral agents and are unsuitable as routine empiric therapy for mild cases. Clinical antimicrobial selection should balance disease severity, availability of oral agents, and susceptibility results, avoiding the non-indicated escalation to injectable third-generation cephalosporins and the resultant overuse of antimicrobials.

Conclusions

Hi respiratory tract infections in hospitalized children at our center exhibit a winter–spring bimodal epidemic pattern, with a progressive age shift toward older children. Males account for the majority of cases, but the sex gap narrows over time. Pathogen co-detection is common, with distinct profiles across age groups and seasons.

Local sputum Hi isolates show high resistance to ampicillin and trimethoprim-sulfamethoxazole, whereas third-generation cephalosporins and carbapenems demonstrate favorable in vitro susceptibility and are appropriate alternatives for moderate-to-severe infections. Clinical anti-infective therapy should be guided by ongoing local pathogen surveillance and susceptibility testing, with individualized prescribing based on disease severity, to reduce unnecessary antimicrobial use and slow the spread of resistant strains.

Study Limitations

This was a single-center retrospective study limited to hospitalized children, which may introduce selection bias. Only respiratory tract isolates were analyzed; invasive isolates from blood and cerebrospinal fluid were not included. The study relied exclusively on laboratory surveillance data without clinical outcome information, precluding analysis of the association between resistance phenotypes and treatment response. Serotyping and molecular resistance genotyping were not performed, limiting mechanistic insights into the age shift and resistance evolution. Future multicenter studies integrating molecular typing and clinical outcomes are warranted for a more comprehensive investigation.

Author Contributions

X.L,T.Z, Drafted the manuscript with Xl. X. L S. , T.Z, M.L., and X.l. S. conducted statistical analysis and participated in the design. X. L, T.Z participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. XL. S and T.Z have equal contributions as co-first authors. M. L has the same contribution as X.L and serves as a co-corresponding author. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kunming Children’s Hospital (IEC-C-008-A07-V3.0)

Informed Consent Statement

Our study was approved by the Kunming Children's Hospital Institutional Review Board (Approval No. 2023-03-315-k01). Guardian informed consent was waived by the Kunming Children's Hospital Institutional Review Board due to the retrospective nature of the study and the use of anonymized clinical data.

Data Availability Statement

The data presented in this study are not publicly available. Anonymized data can be obtained from the corresponding author upon reasonable request and appropriate authorization.

Conflicts of Interest

The authors declare no conflicts of interest.

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