Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Macrolide Resistance of *Mycoplasma pneumoniae* Among Children in Hangzhou: A 2024–2025 Post-Pandemic Surveillance Study

Xudong Xu[1], Xiangyang Xiao[2], Jun Zhou[1], Xinfeng Zhao[1]

[1]Department of Laboratory Medicine, Hangzhou Children's Hospital, Hangzhou, 310014, People's Republic of China; [2]Department of Laboratory Medicine, Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, 310021, People's Republic of China

Correspondence: Xudong Xu, Department of Laboratory Medicine, Hangzhou Children's Hospital, 195 Wenhui Road, Hangzhou, 310021, People's Republic of China, Email xxdtc123@qq.com

Purpose: The COVID-19 pandemic and associated non-pharmaceutical interventions (NPIs) have profoundly altered the circulation patterns of respiratory pathogens globally. In the context of the relaxation of these measures, a marked resurgence of *Mycoplasma pneumoniae* (MP) infections has been observed across China. This study aimed to characterize the epidemiological features and macrolide resistance profile of MP infections among children in Hangzhou during the post-pandemic period (2024–2025), providing laboratory surveillance data to inform clinical management.

Patients and Methods: We conducted a retrospective analysis of 12,380 respiratory specimens from pediatric patients at Hangzhou Children's Hospital (March 2024 to December 2025). MP nucleic acid and the 23S rRNA A2063G/A2064G resistance mutations were detected using quantitative PCR. Positivity and resistance rates were analyzed across gender, age, care setting (inpatient/outpatient), and temporal dimensions.

Results: The overall MP positivity rate was 19.98% (2,473/12,380). Among positive cases, 86.94% (2,150/2,473) carried resistance mutations-representing one of the highest resistance levels documented globally. Critically, outpatients exhibited significantly higher resistance rates than inpatients (92.13% vs 86.10%; χ^2=11.89, P<0.01), despite comprising only 9.2% of tested patients. Positivity rates showed no significant gender disparity (19.58% vs 20.41%, P>0.05). Age distribution followed a unimodal pattern, peaking in school-aged children (6–12 years: 27.90%-39.08%), while resistance rates exceeded 78% across all age groups-notably reaching 92.86% even in infants (<1 year). Monthly resistance rates in 2024 ranged from 74.89% to 94.20%, escalating to 100% in April and June 2025.

Conclusion: This post-pandemic laboratory surveillance reveals alarmingly high and persistently elevated macrolide resistance in pediatric MP infections in Hangzhou, with significantly higher resistance burdens in outpatients. The universal high resistance across all pediatric ages-including infants-suggests widespread community circulation of resistant strains. These findings underscore the urgent need for rapid resistance testing and antimicrobial stewardship programs specifically targeting outpatient pediatric settings in the post-pandemic era.

Keywords: *Mycoplasma pneumoniae*, macrolide resistance, children, outpatient surveillance, post-COVID-19, antimicrobial stewardship, China

Introduction

Mycoplasma pneumoniae (MP) is a leading causative agent of community-acquired pneumonia (CAP) in children worldwide, responsible for 10–40% of CAP cases during epidemic cycles that typically recur every 3–7 years.[1] Macrolides have long been the first-line treatment for MP infections in children due to their favorable safety profile and efficacy.[2] However, since the initial identification of macrolide-resistant MP (MRMP) in Japan in 2000, resistance has spread rapidly across Asia, Europe, and North America.[3] In China, MRMP rates have surged dramatically, reaching 80–100% in many regions and posing significant challenges to clinical management.[4,5]

https://doi.org/10.2147/IDR.S607500
Received: 16 March 2026
Accepted: 21 May 2026
Published: 26 May 2026

The emergence of macrolide resistance in MP is primarily mediated by point mutations in domain V of the 23S rRNA gene, with A2063G and A2064G being the most prevalent mutations in Chinese isolates.[6] MRMP infection often results in prolonged fever, extended duration of antibiotic use, increased requirement for second-line antibiotics and glucocorticoids, and elevated risk of complications and sequelae.[7] In response to this growing threat, Chinese pediatric respiratory experts formulated the Expert consensus on the diagnosis and treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children in 2024, providing evidence-based guidance for clinical management.[8,9]

The COVID-19 pandemic and the implementation of non-pharmaceutical interventions (NPIs) have fundamentally disrupted the transmission dynamics of respiratory pathogens worldwide.[10,11] Multiple studies have documented that during the pandemic (2020–2022), MP incidence declined dramatically to as low as 1.69% coincident with these measures.[12] Meanwhile, inappropriate antibiotic use during the pandemic further accelerated the development of antimicrobial resistance in various bacterial pathogens.[13,14] In the context of the relaxation of NPIs in China after December 2022, a marked resurgence of MP infections has been observed across multiple regions, with infection rates rebounding to 19.4–35.9% in 2023.[15,16] Studies from Henan Province documented MP positivity increasing from 12.56% in 2022 to 35.01% in 2023, with MRMP rates escalating from 46.74% pre-pandemic to 83.31% post-pandemic.[17] Genomic surveillance has revealed that the resurgence is primarily driven by clonal expansion of P1-1 genotype strains with near-universal macrolide resistance mutations.[18,19]

While numerous studies have characterized MP epidemiology in hospitalized children across various Chinese regions,[20,21] there remains a critical gap in understanding resistance patterns in outpatient settings, where empirical antibiotic prescribing is most prevalent and diagnostic testing is least accessible. This distinction is particularly important given that outpatient resistance rates may more accurately reflect circulating community strains.

Hangzhou, the capital city of Zhejiang Province in eastern China, has a permanent resident population exceeding 12.37 million, with children aged 0–14 years accounting for approximately 12.9% of the total population.[22] Understanding the local resistance landscape-particularly the differences between inpatient and outpatient populations and across age strata-is essential for guiding empirical treatment decisions, optimizing antimicrobial stewardship, and informing public health policy in the post-pandemic era.[23]

This single-center laboratory-based surveillance study analyzes MP positivity and macrolide resistance mutations among 12,380 children tested at Hangzhou Children's Hospital from March 2024 to December 2025. We aimed to: (a) characterize post-pandemic MP epidemiology and resistance patterns; (b) compare resistance burdens between inpatient and outpatient settings; (c) examine age-specific variations in infection and resistance; (d) assess temporal trends over the two-year surveillance period.

Patients and Methods

Study Design and Participants

This retrospective laboratory-based surveillance study included 12,380 pediatric patients with respiratory infections who underwent MP nucleic acid testing at Hangzhou Children's Hospital from March 2024 to December 2025. As a single-center surveillance study, this analysis describes resistance patterns among tested specimens and does not aim to calculate population-based incidence rates.

Inclusion criteria: (a) age ≥1 month and <18 years; (b) clinical diagnosis of CAP or suspected MP infection based on presenting symptoms (fever, cough, wheezing, or radiographic evidence of pneumonia); (c) complete MP nucleic acid and resistance mutation testing; (d) availability of basic demographic information (age, gender, care setting).

Exclusion criteria: (a) age <1 month; (b) severe comorbidities unrelated to respiratory infection (eg., immunodeficiency, congenital heart disease, malignancy); (c) incomplete testing data; (d) repeat testing within 14 days of a positive result (only the first positive test was included);[24] (e) age ≥18 years old.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee (Institutional Review Board) of Hangzhou Children's Hospital (Approval No.: IRB2026016 (IIT)). The requirement for

informed consent was waived due to the retrospective nature of the study. All patient data were used confidentially and analyzed anonymously in compliance with medical data protection regulations.

Laboratory Detection

Nasopharyngeal swabs or sputum samples were collected according to standard protocols upon admission (for inpatients) or at the time of outpatient consultation. After collection, swabs were immediately placed into universal transport media and stored at 2–8°C until processing within 24 hours.

Nucleic acids were extracted using a thermal lysis kit (DaAn Gene Co., Ltd., Guangzhou, People's Republic of China) following the manufacturer's instructions. MP detection and resistance mutation analysis were performed simultaneously using a commercial quantitative PCR assay (Mole Biotechnology Co., Ltd., Jiangsu, People's Republic of China) targeting the MP P1 gene and the 23S rRNA A2063G/A2064G point mutations-the two most prevalent macrolide resistance determinants in China.[25] Amplification was conducted on an ABI-7500 Fast Dx system (Applied Biosystems, Foster City, CA, USA) with the following thermal cycling conditions: 95°C for 3 minutes, followed by 45 cycles of 95°C for 15 seconds and 60°C for 30 seconds.

A sample was considered MP-positive if the P1 gene cycle threshold (Ct) value was <35.01, and macrolide-resistant if the mutation-specific Ct value was <35.33, as per the manufacturer's validated cutoffs. Positive and negative controls were included in each run to ensure assay validity.[26]

Statistical Analysis

Data were analyzed using R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are presented as frequencies and percentages, with group comparisons performed using the Chi-square (χ^2) test or Fisher's exact test, as appropriate. Wilson score method was used to calculate 95% confidence intervals for proportions.

For age-based analyses, we categorized children into single-year age groups to preserve granularity while also summarizing by developmental stages: infants (<1 year), toddlers (1–2 years), preschool (3–5 years), school-aged (6–12 years), and adolescents (13–17 years). MP surveillance periods were defined as calendar years (January-December) for 2024 and 2025.

Multivariate logistic regression was used to examine factors associated with MP positivity and resistance. Statistical significance was set at a two-tailed P value <0.05.

Results

Characteristics of the Study Population

From March 2024 to December 2025, a total of 12,380 pediatric patients with respiratory infections were enrolled and tested for MP. The demographic and clinical characteristics of the study population are summarized in Table 1. The cohort included 6,497 males (52.5%) and 5,883 females (47.5%), with a median age of 5 years (interquartile range [IQR]: 2–8 years). Inpatients constituted 90.8% (11,235/12,380) of the tested population, while outpatients accounted for 9.2% (1,145/12,380).

Table 1 Overall Detection of *Mycoplasma pneumoniae* and Macrolide Resistance Mutations (March 2024-December 2025)

Indicator	Number of Cases	Proportion (%)	95% CI
Total Tested	12,380	100.00	–
MP-Positive	2,473	19.98	19.3–20.7
Resistance-Positive*	2,150	86.94	85.5–88.3
MP-Negative	9,907	80.02	79.3–80.7

Note: *Resistance rate calculated as number of resistance-positive cases divided by number of MP-positive cases.
Abbreviation: CI, confidence interval.

Overall MP Positivity and Resistance Rates

Among 12,380 tested patients, 2,473 (19.98%; 95% confidence interval [CI]: 19.3%-20.7%) were MP-positive. Of these, 2,150 (86.94%; 95% CI: 85.5%-88.3%) harbored macrolide resistance mutations (Table 1). The overall positivity rate remained relatively stable across the two-year surveillance period, with 19.6% in 2024 and 20.5% in 2025 (P=0.21).

Gender Distribution

No significant differences in MP positivity or resistance rates were observed between males and females. Among 6,497 males tested, 1,272 (19.58%) were MP-positive, with 1,121 (88.13%) harboring resistance mutations. Among 5,883 females, 1,201 (20.41%) were MP-positive, with 1,029 (85.68%) resistant (both P>0.05) (Table 2). This absence of gender disparity is consistent with findings from multicenter studies across China 17,19, and is further illustrated by age- and sex-stratified positivity and resistance rates in Supplementary Figure S1.

Inpatient-Outpatient Disparity

Outpatients demonstrated significantly higher MP positivity and resistance rates compared to inpatients. Among 1,145 outpatients tested, 343 (29.96%; 95% CI: 27.3%-32.7%) were MP-positive-substantially higher than the 18.96% (2,130/11,235; 95% CI: 18.2%-19.7%) observed in inpatients (χ^2=74.32, P<0.01). More critically, the resistance rate among MP-positive outpatients reached 92.13% (316/343; 95% CI: 88.8%-94.7%), significantly exceeding the 86.10% (1,834/2,130; 95% CI: 84.6%-87.5%) seen in inpatients (χ^2=11.89, P<0.01) (Table 3 and Figure 1). This disparity persisted despite outpatients comprising only 9.2% of the total tested population.

Age Distribution

MP positivity exhibited a distinct unimodal age distribution (Table 4 and Figure 2). The positivity rate was lowest in infants <1 year (4.02%; 28/697) and progressively increased with age, peaking in school-aged children: 6 years (27.90%; 358/1,283), 7 years (30.11%; 333/1,106), 8 years (34.12%; 290/850), 9 years (37.26%; 237/636), 10 years (36.56%; 204/558), and 11 years (39.08%; 161/412). Positivity then declined in adolescents aged 12–17 years (12.2%-21.7%). This age distribution pattern aligns closely with pre-pandemic epidemiological studies showing highest susceptibility in school-aged children.[1,17,20]

Remarkably, macrolide resistance rates remained exceptionally high across all pediatric age groups, exceeding 78% in every stratum and surpassing 85% in most groups aged 3–12 years (Table 4 and Figure 2). Notably, even infants

Table 2 Detection Rates of MP and Macrolide Resistance by Gender

Gender	Tested (n)	MP-Positive n (%)	95% CI	Resistance-Positive n (%)*	95% CI
Male	6,497	1,272 (19.58)	18.6–20.6	1,121 (88.13)	86.2–89.9
Female	5,883	1,201 (20.41)	19.4–21.5	1,029 (85.68)	83.6–87.6
Total	12,380	2,473 (19.98)	19.3–20.7	2,150 (86.94)	85.5–88.3

Note: *Resistance rate calculated as in Table 1.
Abbreviation: CI, confidence interval.

Table 3 Detection Rates of MP and Macrolide Resistance by Care Setting

Setting	Tested (n)	MP-Positive n (%)	95% CI	Resistance-Positive n (%)*	95% CI
Inpatient	11,235	2,130 (18.96)	18.2–19.7	1,834 (86.10)	84.6–87.5
Outpatient	1,145	343 (29.96)	27.3–32.7	316 (92.13)	88.8–94.7
Total	12,380	2,473 (19.98)	19.3–20.7	2,150 (86.94)	85.5–88.3

Note: *Resistance rate calculated as in Table 1.
Abbreviation: CI, confidence interval.

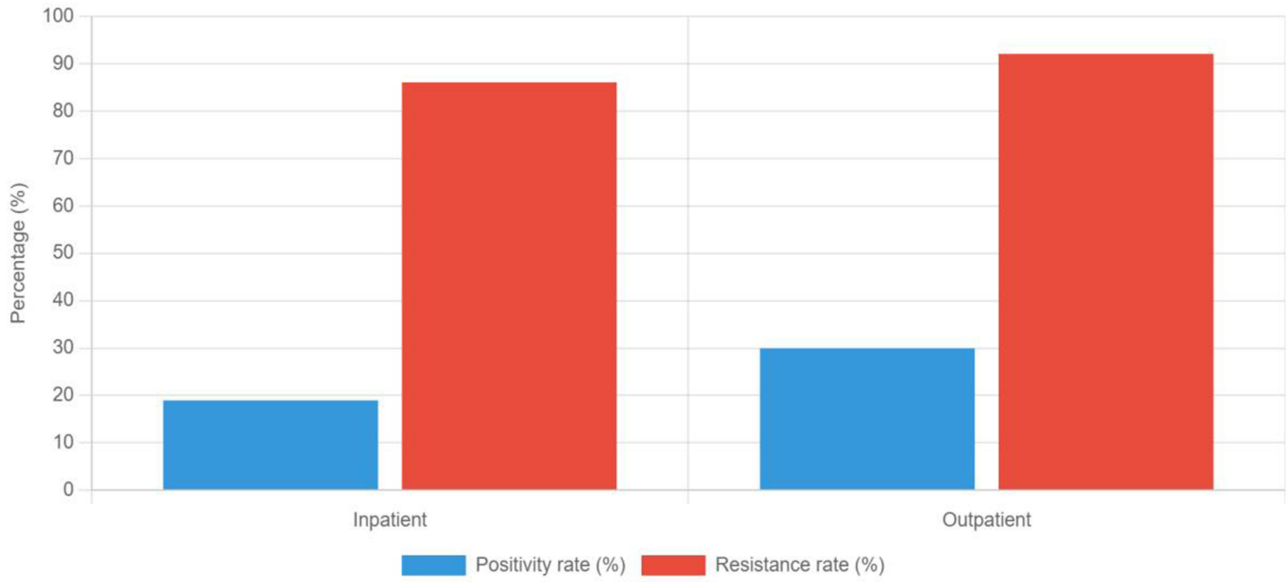

Figure 1 Comparison of MP positivity and macrolide resistance rates between inpatients and outpatients. Outpatients showed significantly higher positivity (29.96% vs 18.96%, *P*<0.01) and resistance rates (92.13% vs 86.10%, *P*<0.01). Error bars represent 95% confidence intervals.

(<1 year) demonstrated a 92.86% (26/28) resistance rate-among the highest observed-suggesting widespread community circulation of resistant strains and potential transmission from older siblings or caregivers. Linear regression analysis revealed no significant trend in resistance rates across age groups (*P* for trend = 0.34), indicating uniformly high resistance burden throughout childhood.

Table 4 Detection Rates of MP and Macrolide Resistance by Age Group

Age (years)	Tested (n)	MP-Positive n (%)	95% CI	Resistance-Positive n (%)*	95% CI
<1	697	28 (4.02)	2.7–5.8	26 (92.86)	76.5–99.1
1	1,062	67 (6.31)	4.9–8.0	54 (80.60)	69.1–89.2
2	1,092	91 (8.33)	6.8–10.1	72 (79.12)	69.4–86.8
3	1,526	157 (10.29)	8.8–11.9	141 (89.81)	84.0–94.0
4	1,353	195 (14.41)	12.6–16.4	168 (86.15)	80.5–90.7
5	1,177	223 (18.95)	16.8–21.3	189 (84.75)	79.3–89.2
6	1,283	358 (27.90)	25.5–30.4	314 (87.71)	83.9–90.9
7	1,106	333 (30.11)	27.4–32.9	298 (89.49)	85.8–92.5
8	850	290 (34.12)	30.9–37.4	256 (88.28)	84.0–91.7
9	636	237 (37.26)	33.5–41.1	205 (86.50)	81.4–90.6
10	558	204 (36.56)	32.5–40.8	179 (87.75)	82.5–91.9
11	412	161 (39.08)	34.3–44.0	139 (86.34)	80.0–91.2
12	267	58 (21.72)	16.9–27.2	52 (89.66)	78.9–96.1
13	174	37 (21.26)	15.5–28.1	30 (81.08)	64.8–92.0
14	109	23 (21.10)	13.9–30.0	18 (78.26)	56.3–92.5
15	49	6 (12.24)	4.6–24.8	4 (66.67)	22.3–95.7
16	24	4 (16.67)	4.7–37.4	4 (100.00)	39.8-100
17	5	1 (20.00)	0.5–71.6	1 (100.00)	2.5–100

Note: *Resistance rate calculated as in Table 1.
Abbreviation: CI, confidence interval.

https://doi.org/10.2147/IDR.S607500

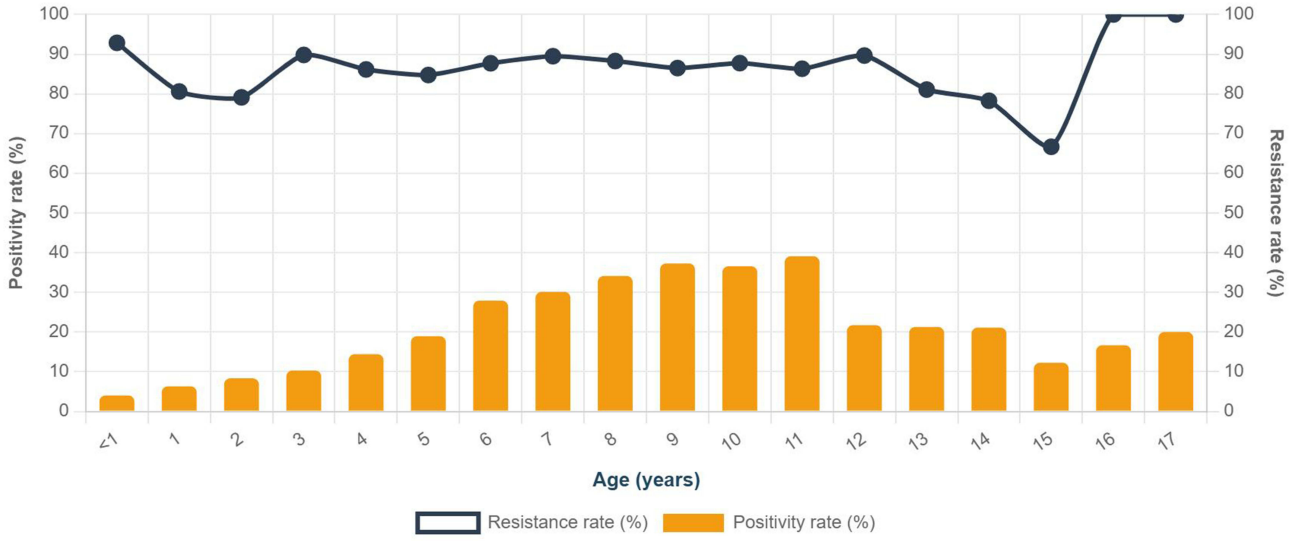

Figure 2 Age distribution of MP positivity (bars) and macrolide resistance (line with points). Positivity followed a unimodal distribution, peaking in children aged 6–12 years (27.90%-39.08%). Resistance rates remained >78% across all age groups, with the highest rates observed in infants (92.86%) and children aged 3–12 years (>85%).

Temporal Trends

2024 Season: In 2024 (March-December), MP positivity showed a distinct seasonal pattern, with cases peaking from March through July. The highest monthly positive counts occurred in July (381 cases) and May (321 cases). Monthly resistance rates ranged from 74.89% (August) to 94.20% (March), with consistently elevated resistance (>83%) throughout most of the year (detailed monthly data are provided in Table 5 and Figure 3).

2025 Season: In 2025, MP activity continued with notable fluctuations. Resistance rates reached 100% in both April (12/12 cases) and June (13/13 cases)-a striking finding consistent with reports from other Chinese regions where MRMP rates have approached 100% in certain periods.[18,19] Resistance remained above 80% in most months, with the exception of September-November where rates dipped to 66.67%-70.00% (based on 6–10 positive cases per month) (Table 5 and Figure 3).

The persistence of high resistance rates (>85% in 17 of 22 months with data) throughout the surveillance period indicates that macrolide-resistant MP has become the dominant circulating genotype in this region, mirroring national trends documented in multicenter studies.[16,17]

Table 5 Monthly Detection Rates of MP and Macrolide Resistance in 2024 and 2025

Month	2024: MP+ (n)	2024: Res+ (n)	2024: Res Rate (%)	95% CI	2025: MP+ (n)	2025: Res+ (n)	2025: Res Rate (%)	95% CI
Jan	–	–	–	–	92	79	85.87	77.1–92.3
Feb	–	–	–	–	29	24	82.76	64.2–94.2
Mar	138	130	94.20	88.9–97.5	19	17	89.47	66.9–98.7
Apr	207	194	93.72	89.5–96.7	12	12	100.00	73.5-100
May	321	282	87.85	83.8–91.2	7	6	85.71	42.1–99.6
Jun	264	220	83.33	78.3–87.6	13	13	100.00	75.3-100
Jul	381	329	86.35	82.5–89.6	14	13	92.86	66.1–99.8
Aug	223	167	74.89	68.7–80.4	12	11	91.67	61.5–99.8
Sep	119	102	85.71	78.2–91.4	10	7	70.00	34.8–93.3
Oct	170	150	88.24	82.5–92.7	6	4	66.67	22.3–95.7
Nov	228	202	88.60	83.8–92.4	6	4	66.67	22.3–95.7
Dec	189	173	91.53	86.7–95.1	13	11	84.62	54.6–98.1

Note: CI, confidence interval calculated using the Wilson score method.

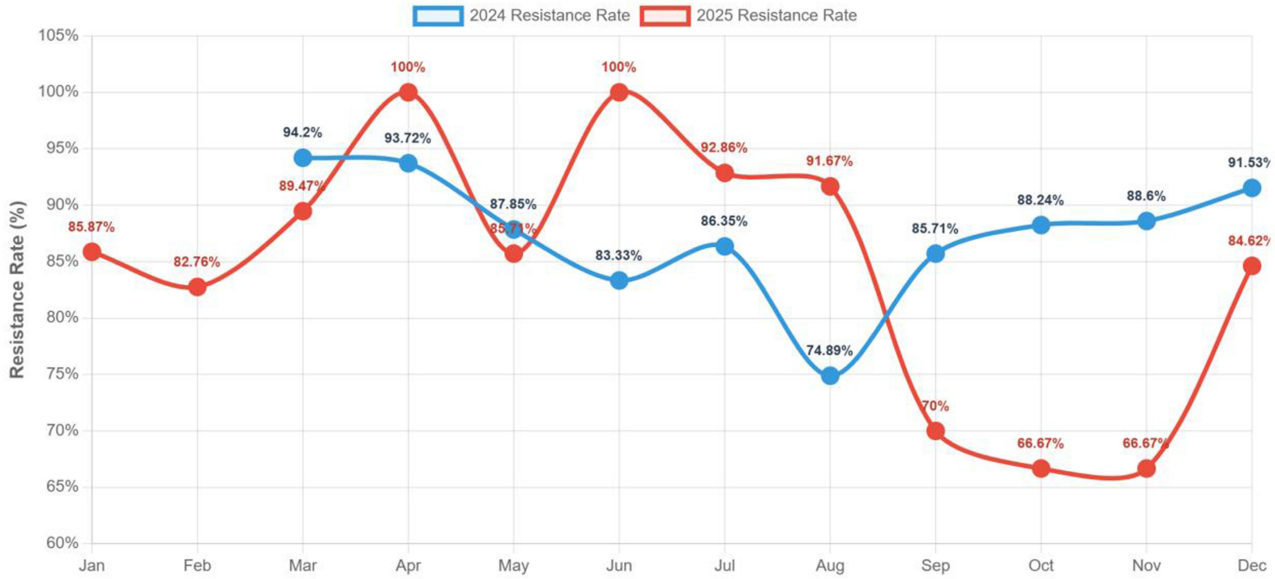

Figure 3 Monthly macrolide resistance rates in 2024 and 2025 with 95% confidence intervals. Resistance remained elevated throughout the surveillance period, reaching 100% in April and June 2025. Shaded area represents period without 2024 data collection (January-February).

Discussion

This single-center laboratory surveillance study provides a comprehensive snapshot of the macrolide resistance landscape of *Mycoplasma pneumoniae* among children in Hangzhou during the 2024–2025 post-pandemic period. Our analysis of 12,380 pediatric specimens reveals several critical findings that have immediate implications for clinical practice and public health policy.

Overall Resistance Burden in National Context

The overall macrolide resistance rate of 86.94% places Hangzhou among regions with the highest documented MP resistance globally, consistent with the alarming nationwide trend in China. This figure closely aligns with recent multicenter studies: a 2023–2024 analysis of 421 strains from four Chinese regions (Liaoning, Zhejiang, Wuhan, Guizhou) reported 97.1% macrolide resistance;[16] surveillance in Henan Province from 2017–2024 documented MRMP rates increasing from 36.68% in 2018 to 87.16% in 2023;[17] and a study in Urumqi (2023–2024) found 99.1% resistance among pediatric CAP cases.[18] The dominance of the A2063G mutation (accounting for 98.2% of resistant cases in the Urumqi study)[18] is consistent with our detection method targeting this primary resistance mechanism.

Genomic epidemiological studies have revealed that the post-pandemic resurgence is driven by clonal expansion of specific resistant lineages. Wang et al demonstrated that ST3 (P1-1 genotype) strains maintained 100% macrolide resistance in Beijing, while ST14 resistance increased rapidly.[19] Similarly, Jiao et al identified that the 4-5-7-2 genotype (P1-1 lineage) became dominant post-pandemic, enriched with virulence and metabolism-related genes that may confer fitness advantages.[5] These findings help explain the sustained high resistance rates observed in our study despite monthly fluctuations in case counts.

The striking contrast between Chinese MRMP rates (>85%) and contemporaneous surveillance from the United States (0–8.7% in Ohio, 2023–2025)[27] reflects fundamental differences in antibiotic prescribing practices and antimicrobial stewardship. Macrolides remain first-line empirical therapy for pediatric CAP in China due to their favorable safety profile, oral bioavailability, and coverage of atypical pathogens.[28] This practice, combined with high outpatient antibiotic prescribing rates and limited access to rapid diagnostic testing, creates intense selective pressure favoring resistant strains.[29]

https://doi.org/10.2147/IDR.S607500

Age Distribution and Universal Resistance

The unimodal age distribution of MP positivity-peaking in school-aged children (6–12 years) and lowest in infants-aligns with established epidemiological patterns documented over decades.[1,17,20] This likely reflects school-based transmission dynamics and the gradual waning of maternal antibodies, while infants may be partially protected by limited exposure and residual passive immunity.[30] The consistency of this finding with pre-pandemic literature validates our laboratory methods and sampling approach.

However, a more concerning observation is the uniformly high resistance rates across all pediatric age groups. The finding that even infants (<1 year) demonstrate a 92.86% resistance rate is particularly alarming, as it suggests: (a) widespread community circulation of resistant strains; (b) potential transmission from infected older siblings or caregivers; (c) the futility of empirical macrolide monotherapy even in the youngest patients.This universal high resistance burden across all ages represents a fundamental shift from historical patterns where resistance was primarily concentrated in older children with greater antibiotic exposure.[31]

The Outpatient-Inpatient Disparity: A Critical Sentinel Finding

The significantly higher resistance rate in outpatients (92.13% vs 86.10%, P<0.01) represents our most clinically relevant and actionable finding. Several factors may explain this disparity. First, outpatients likely represent earlier, milder community-acquired infections, whereas inpatients may include more severe cases, nosocomial infections, or patients with comorbidities that could influence healthcare-seeking behavior and antibiotic exposure history. Second, the higher resistance rate in outpatients may reflect greater selective pressure from empirical macrolide use in primary care settings, where diagnostic testing is less frequently performed and antibiotics are often prescribed presumptively for febrile respiratory illnesses. Third, outpatients may be more representative of circulating community strains, while inpatients could be enriched for specific subpopulations.

Notably, the outpatient resistance rate of 92.13% suggests that empirical macrolide monotherapy for suspected MP pneumonia in the community is highly likely to fail. This finding has immediate clinical implications and supports the integration of rapid molecular resistance testing into outpatient settings, particularly during peak MP seasons. The 2024 Chinese expert consensus on MRMP diagnosis and treatment emphasizes that early identification of resistance through molecular testing can guide appropriate antibiotic selection and improve outcomes.[8,9]

Temporal Trends and Post-Pandemic Dynamics

The monthly resistance rates observed in our study-ranging from 74.89% to 100%-demonstrate the persistent circulation of resistant strains throughout the post-pandemic period. The extreme values reaching 100% in April and June 2025, while based on smaller sample sizes (12–13 positive cases), nevertheless signal the continued dominance of resistant genotypes.

Comparisons with pre-pandemic MP resistance data from Hangzhou would have been valuable to assess the impact of COVID-19-related NPIs on resistance dynamics. However, studies from other Chinese regions have documented increasing resistance trends over the past decade, with acceleration noted in the post-pandemic period.[17,18] The relaxation of NPIs in Hangzhou from mid-2020 onward likely facilitated the re-emergence and widespread circulation of resistant strains that persisted in the community during periods of reduced respiratory pathogen transmission.[15,16]

The experience with respiratory pathogens in the post-pandemic period provides instructive parallels. Studies from Xi'an documented MP increasing from 4.35% during the pandemic to 11.21% post-pandemic, with co-infection rates rising from 4.05% to 11.55%.[13] Similarly, research from multiple Chinese cities has documented altered seasonality and shifts in age distribution for various respiratory pathogens following NPI relaxation.[20,21]

Novel Antimicrobial Strategies to Combat Resistance

Given the extremely high macrolide resistance rate, innovative therapeutic strategies are urgently needed to treat drug-resistant MP infections. Emerging approaches include the Trojan horse antibiotic delivery system, targeting bacterial metallophores, and phage therapy, which offer pathogen-specific alternatives to conventional antibiotics.[32–35]

Clinical and Public Health Implications

Our findings have several important implications for clinical practice and public health policy. First, the extraordinarily high resistance rates-particularly in outpatients-support a reconsideration of empirical treatment algorithms for suspected MP pneumonia in this region. The 2024 Chinese expert consensus recommends that in areas with high MRMP prevalence (>50%), alternative antibiotics such as tetracyclines (doxycycline in children ≥8 years) or fluoroquinolones should be considered when resistance is suspected or confirmed, weighing benefits against potential adverse effects.[8,9]

Second, the integration of rapid molecular point-of-care testing for resistance mutations into outpatient settings should be prioritized. Such testing can guide appropriate antibiotic selection, reduce treatment failures, and potentially slow the spread of resistant strains. Studies have demonstrated that rapid resistance testing can lead to timely adjustments in antibiotic therapy and improved clinical outcomes.[26]

Third, enhanced antimicrobial stewardship programs targeting primary care settings are urgently needed. Educational interventions for healthcare providers, coupled with public awareness campaigns about appropriate antibiotic use, may help mitigate further resistance selection.[29] The stark contrast between MRMP rates in China and the United States underscores the potential impact of stewardship efforts.

Study Limitations

Several important limitations should be acknowledged.(a) This is a single-center study conducted at a children's hospital in Hangzhou, and findings may not be generalizable to other hospitals, primary care settings, or regions within China. The overrepresentation of inpatients (90.8%) in our tested population reflects hospital-based testing patterns and may not reflect community prevalence.(b) The lack of linked clinical data prevents correlation of resistance with treatment outcomes, disease severity, duration of illness, prior antibiotic exposure, or subsequent clinical response. This represents a critical next step for research.(c) Our sample is limited to patients who sought care and underwent testing at our hospital, introducing potential selection bias. Asymptomatic carriers, mild cases not presenting for care, and patients managed entirely in primary care settings are not represented.(d) Our molecular assay detects only the two most common resistance mutations (A2063G/A2064G) and may miss rare or novel resistance mechanisms. However, these mutations account for >95% of macrolide resistance in Chinese MP isolates.[18,25](e) We lacked access to outpatient antibiotic prescribing data, which could provide direct insights into the drivers of resistance.(f) The retrospective design precludes establishment of causal relationships; the observed association between outpatient status and higher resistance should be interpreted as hypothesis-generating rather than definitive.

Future Directions

Our findings highlight several priorities for future research and public health action: (a) Multicenter surveillance across diverse geographic regions within China to assess heterogeneity in resistance patterns and identify local drivers.[16,17](b) Integration of clinical outcomes data through prospective cohort studies to quantify the impact of macrolide resistance on treatment failure, hospitalization duration, complication rates, and healthcare costs.[7] (c) Molecular epidemiology studies using whole-genome sequencing to characterize circulating MP clones, track transmission networks, and identify potential fitness determinants associated with resistant strains.[5,19](d) Intervention studies evaluating the impact of rapid point-of-care resistance testing on antibiotic prescribing, clinical outcomes, and cost-effectiveness in outpatient settings.[26](e) Antimicrobial stewardship interventions targeting primary care providers, including educational initiatives, clinical decision support tools, and audit-feedback systems.[29]

Conclusion

This laboratory-based surveillance study reveals an exceptionally high rate of macrolide-resistant *Mycoplasma pneumoniae* (86.94%) among children tested at a Hangzhou hospital during the 2024–2025 post-pandemic period. Critically, resistance was significantly higher in outpatients (92.13%) than in inpatients (86.10%), and remained uniformly elevated (>78%) across all pediatric ages-including infants-suggesting widespread community circulation of resistant strains.

These findings suggest that empirical macrolide monotherapy for suspected MP pneumonia in this region is highly likely to fail.

Our results align with the growing body of evidence documenting the post-pandemic resurgence of MRMP across China[16–18] and underscore the urgent need for updated treatment guidelines, enhanced surveillance systems, and robust antimicrobial stewardship programs.[8,9] We advocate for: (a) integration of rapid point-of-care PCR testing for resistance mutations into routine outpatient care; (b) enhanced antimicrobial stewardship programs specifically targeting primary care settings where most empirical prescribing occurs; (c) reconsideration of empirical treatment algorithms for pediatric CAP in regions with high MRMP prevalence; (d) multicenter surveillance networks to monitor resistance trends and inform region-specific guidelines.

The COVID-19 pandemic has fundamentally altered the epidemiology of respiratory pathogens worldwide. As we navigate the post-pandemic era, understanding and responding to these changes-including the alarming resistance patterns documented here-will be essential for optimizing child health outcomes and preserving antibiotic effectiveness for future generations.

Acknowledgments

The authors thank the staff of the Department of Laboratory Medicine at Hangzhou Children's Hospital for assistance with specimen processing and data collection. A preprint version of this manuscript was deposited on Research Square.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Waites KB, Xiao L, Liu Y, Balish MF, Atkinson TP. *Mycoplasma pneumoniae* from the respiratory tract and beyond. *Clin Microbiol Rev*. 2017;30(3):747–809. doi:10.1128/CMR.00114-16
2. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America. *Clin Infect Dis*. 2011;53(7):e25–e76. doi:10.1093/cid/cir531
3. Okada T, Morozumi M, Tajima T, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. *Clin Infect Dis*. 2012;55(12):1642–1649. doi:10.1093/cid/cis784
4. Zhao F, Liu G, Wu J, et al. Surveillance of macrolide-resistant *Mycoplasma pneumoniae* in Beijing, China, from 2008 to 2019. *Antimicrob Agents Chemother*. 2020;64(8):e00322–20.
5. Jiao W, Xu S, Chen F, et al. Genomic analysis of *Mycoplasma pneumoniae* resurgence in children after the COVID-19 pandemic in China. *Lancet Reg Health West Pac*. 2025;59:101456.
6. Zhang Z, Dou H, Yuan Q, et al. Proteomic and phenotypic studies of *Mycoplasma pneumoniae* revealed macrolide-resistant mutation (A2063G) associated changes in protein composition and pathogenicity of type I strains. *Microbiol Spectr*. 2023;11(4):e00323.
7. Yu C, Lü W, Zhang XY. Relationship between clinical phenotype and chest imaging in children with community-acquired pneumonia with MP 23S rRNA A2063G gene variation. *J Clin Pediatr*. 2021;39(4):265–268.
8. Wang Y-S, Zhou Y-L, Bai G-N, et al. Expert consensus on the diagnosis and treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children. *World J Pediatr*. 2024;20(9):901–914. doi:10.1007/s12519-024-00831-0
9. Wang YS, Zhuang H. Interpretation of the expert consensus on diagnosis and treatment of pediatric macrolide-resistant *Mycoplasma pneumoniae* pneumonia. *Chin J Pract Pediatr*. 2025;40(8):652–655.
10. Sullivan SG, Carlson S, Cheng AC, et al. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. *Euro Surveill*. 2020;25(47):2001847. doi:10.2807/1560-7917.ES.2020.25.47.2001847
11. Williams TC, Sinha I, Barr IG, Zambon M. Transmission of paediatric respiratory syncytial virus and influenza in the wake of the COVID-19 pandemic. *Euro Surveill*. 2021;26(29):2100186. doi:10.2807/1560-7917.ES.2021.26.29.2100186
12. Li ZJ, Yu LJ, Zhang HY, et al. Broad impacts of coronavirus disease 2019 (COVID-19) pandemic on acute respiratory infections in China: an observational study. *Clin Infect Dis*. 2022;75(1):e1054–e1062. doi:10.1093/cid/ciab942
13. Haddad N, Bou Raad E, El Helou S, et al. Antibiotic misuse during the COVID-19 pandemic in Lebanon: a cross-sectional study. *J Pharm Policy Pract*. 2022;15(1):45.
14. Tiri B, Sensi E, Marsiliani V, et al. The impact of the COVID-19 pandemic on the antibiotic resistance of Gram-negative pathogens causing bloodstream infections in an intensive care unit. *Antibiotics*. 2021;10(6):706. doi:10.3390/antibiotics10060706
15. Summeren J, Meijer A, Aspelund G, et al. Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the coming summer and autumn/winter? *Euro Surveill*. 2021;26(29):2100639. doi:10.2807/1560-7917.ES.2021.26.29.2100639

16. Zhang M, Wen W, Ma Y, et al. Multicenter analysis of the *Mycoplasma pneumoniae* resurgence in China 2023–2024. *Sci Rep*. 2025;16(1):76. doi:10.1038/s41598-025-29135-7
17. Qi J, Li H, Li H, et al. Epidemiological changes of *Mycoplasma pneumoniae* among children before, during, and post the COVID-19 pandemic in Henan, China, from 2017 to 2024. *Microbiol Spectr*. 2025;13(7):e0312124. doi:10.1128/spectrum.03121-24
18. Li Y, Liang M, Shi Q, et al. Molecular characteristics of macrolide-resistant *Mycoplasma pneumoniae* in children with community-acquired pneumonia in Urumqi, Xinjiang, China in autumn, winter, and spring 2023–2024. *J Infect Public Health*. 2025;18(6):102748. doi:10.1016/j.jiph.2025.102748
19. Wang X, Zhang Y, Li H, et al. Genomic epidemiological analysis reveals new insights into the resurgence of *Mycoplasma pneumoniae* in China. *Front Cell Infect Microbiol*. 2025;15:1456782. doi:10.3389/fcimb.2025.1611519
20. Cai L, Gao XM, Wang ZJ, et al. Distribution and epidemiological characteristics of non-bacterial pathogens in children with acute respiratory infections at 10 regional pediatric medical centers in Fujian Province, 2023-2024. *Chin J Nosocomiol*. 2025;35(12):3701–3706.
21. Jia R, Lu L, Su L, et al. Resurgence of respiratory syncytial virus infection during COVID-19 pandemic among children in Shanghai, China. *Front Microbiol*. 2022;13:938372. doi:10.3389/fmicb.2022.938372
22. Hangzhou Municipal Bureau of Statistics. Hangzhou Statistical Yearbook 2024. Available from: http://tjj.hangzhou.gov.cn. Accessed May 10, 2026.
23. Jonas JA, Acker KP, Thomas C, Yen S, Levine DA. Epidemiology of pediatric viral illnesses before, during, and after the "tripledemic" viral surge. *Pediatr Emerg Care*. 2025;41(9):679–686. doi:10.1097/PEC.0000000000003402
24. Chen Y, Zhao X, Ye C, et al. Epidemiology and viral loads of respiratory syncytial virus in hospitalized children prior to and during COVID-19 pandemic in Hangzhou, China. *J Med Virol*. 2024;96(8):e29855. doi:10.1002/jmv.29855
25. Chuang Y-C, Lin K-P, Wang L-A, Yeh T-K, Liu P-Y. The impact of the COVID-19 pandemic on respiratory syncytial virus infection: a narrative review. *Infect Drug Resist*. 2023;16:661–675. doi:10.2147/IDR.S396434
26. Pan RQ, Meng J, Song JZ. Analysis of epidemiological characteristics and resistance mutation rate of MP infection in children in Nanxun area, 2022-2023. *Gen Pract Investig*. 2025;23(4):355–358.
27. Wang H, Embry T, Everhart K, et al. Macrolide-resistant *Mycoplasma pneumoniae* in children, Ohio, USA. *Emerg Infect Dis*. 2025;31(12):2341–2343. doi:10.3201/eid3112.251008
28. National Health Commission of the People's Republic of China. Guidelines for the diagnosis and treatment of community-acquired pneumonia in children (2024 version). *Chin J Pediatr*. 2024;62(3):201–210.
29. Abu-Raya B, Viñeta Paramo M, Reicherz F, Lavoie PM. Why has the epidemiology of RSV changed during the COVID-19 pandemic? *EClinicalMedicine*. 2023;61:102089. doi:10.1016/j.eclinm.2023.102089
30. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588–598. doi:10.1056/NEJMoa0804877
31. Hasegawa K, Jartti T, Mansbach JM, et al. Respiratory syncytial virus genomic load and disease severity among children hospitalized with bronchiolitis: multicenter cohort studies in the United States and Finland. *J Infect Dis*. 2015;211(10):1550–1559. doi:10.1093/infdis/jiu658
32. Möller N, Lubkowicz D, Groll M, et al. Trojan horse antibiotics: a novel way to circumvent Gram-negative bacterial. *ACS Infect Dis*. 2020;6(8):2279–2292. doi:10.1021/acsinfecdis.0c00403
33. Ballouche M, Cornelis P, Baysse C. Towards new antibiotics classes targeting bacterial metallophores. *Future Microbiol*. 2009;4(8):1007–1021.
34. Zazo H, Colino CI, Lanao JM. Antibiotic conjugates: using molecular Trojan horses to overcome drug resistance. *Expert Opin Drug Discov*. 2020;15(5):557–569.
35. Lin DM, Koskella B, Lin HC. Phage therapy: an alternative to antibiotics in the age of multi-drug resistance. *World J Gastrointest Pharmacol Ther*. 2017;8(3):162–173. doi:10.4292/wjgpt.v8.i3.162