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Comparative epidemiology of serology-defined Mycoplasma pneumoniae positivity,macrolide resistance and co-infection in hospitalised children before and after COVID-19 non-pharmaceutical interventions in Chengdu,China(2021–2025)

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Abstract

Background: China implemented extensive non-pharmaceutical interventions(NPIs)against SARS-CoV-2 from 2020,which reshaped the circulation of respiratory pathogens.After NPIs were relaxed at the end of 2022,Mycoplasma pneumoniae(MP)re-emerged.How MP positivity,macrolide resistance and co-infection changed between the NPI and post-NPI eras in southwest China remains incompletely characterised.

Methods: We retrospectively analysed children aged<18 years tested for MP at a tertiary children's hospital in Chengdu between 1 January 2021 and 31 December 2025(NPI phase 2021–2022;post-NPI phase 2023–2025).The primary outcome was serology-defined MP positivity,measured with a particle-agglutination assay available throughout the study period.Between-phase differences were estimated by multivariable logistic regression adjusted for age group,sex and season,and were re-estimated under alternative serological definitions.Macrolide resistance(from November 2023)and 13-pathogen panel co-infection(from March 2023)were analysed in post-NPI subsets.Environmental associations were assessed by lagged Spearman correlation with Benjamini–Hochberg correction,including first-differenced series.

Results: Among 11,531 MP-tested visits,4,295(37.25%,95%CI 36.37–38.13)were serology-defined MP-positive.Positivity rose from 33.88%(2,041/6,025)during the NPI phase to 40.94%(2,254/5,506)post-NPI(adjusted odds ratio[aOR]1.16,95%CI 1.07–1.26),peaking at 52.30%in 2024.The increase was directionally consistent across definitions and larger under a titre threshold of≥1:160(9.49%vs 24.23%;aOR 2.72,95%CI 2.44–3.05).Positivity increased from 3.97%below 1 year to 56.95%at 6–14 years and peaked in winter(43.23%).Among 929 MP-positive children confirmed by nucleic-acid testing(NAT),80.95%carried macrolide-resistance mutations,and 22.36%of 832 panel-tested MP-positive children had co-infections,most often rhinovirus.Serology and NAT agreed poorly($\kappa=-0.148$).After first-differencing and false-discovery-rate correction,no environmental association remained statistically significant.

Conclusions: Relaxation of NPIs was associated with higher serology-defined MP positivity and a persistently high macrolide-resistance burden in hospitalised children.Absolute positivity is strongly dependent on the serological definition.Apparent environmental associations reflected shared seasonal and secular trends and should not be interpreted causally.

Keywords: Mycoplasma pneumoniae;children;COVID-19;non-pharmaceutical interventions;serology;macrolide resistance;co-infection;environmental correlates

Background

Acute respiratory tract infections remain a leading cause of paediatric morbidity and hospitalisation worldwide.Mycoplasma pneumoniae(MP)is one of the smallest self-replicating prokaryotes,lacks a cell wall,and is a major aetiological agent of community-acquired pneumonia(CAP)in school-aged children[1].Although MP infection is frequently self-limiting,it may progress to severe pneumonia and extrapulmonary manifestations[1].

Macrolides are the first-line therapy for paediatric MP infection.However,the rapid emergence of macrolide-resistant MP(MRMP)has become a global concern[2],with resistance rates frequently exceeding 80%in many regions of China[3,4],and post-pandemic surveillance continues to report burdens approaching 90%[5].The resistance burden therefore directly influences empirical treatment strategies and clinical outcomes in children.

Since early 2020,the COVID-19 pandemic prompted extensive non-pharmaceutical interventions(NPIs),including mask wearing,social distancing,school closures and travel restrictions,which markedly reduced the transmission of SARS-CoV-2 and,concurrently,of many other respiratory pathogens[6].Following the optimisation of COVID-19 control measures at the end of 2022,China entered the post-pandemic era and MP re-emerged with unusual intensity,culminating in a nationwide outbreak in late 2023[7–9].Earlier single-centre work from Chengdu documented the suppression of childhood MP during the early pandemic[10],but did not span the post-NPI rebound,the macrolide-resistance and co-infection landscape,or an appraisal of how the choice of diagnostic assay and positivity threshold shapes the reported epidemiology.

MP positivity is defined operationally by the diagnostic method used.Serology and nucleic-acid testing(NAT)interrogate different biological windows,and serological thresholds(qualitative positivity versus specific antibody titres)differ in sensitivity and specificity[1].Because the reported positivity rate and the magnitude of any between-period difference may therefore depend on the case definition,robustness to alternative definitions is an essential,but frequently neglected,requirement for historical comparisons.

Beyond person-to-person transmission,environmental conditions,including temperature,humidity and ambient air pollutants,may modulate MP activity by affecting host

susceptibility and pathogen survival[11,12].However,because air pollutants and meteorological variables are highly collinear with season and long-term trend,their apparent associations with MP must be examined with methods that account for shared temporal structure and multiple testing.

In this study we retrospectively analysed five years(2021–2025)of MP testing data from hospitalised children in Chengdu,comparing the NPI and post-NPI phases with respect to serology-defined MP positivity,seasonality,age distribution,macrolide resistance,co-infection and pathogen interactions.We explicitly tested the robustness of the phase comparison to alternative serological definitions,and we assessed environmental correlates within a de-trending and multiple-testing framework.Our aim was to provide a rigorous,definition-aware evidence base for post-pandemic MP surveillance and control in southwest China.

Methods

Study design,setting and participants

This retrospective study was conducted at the Department of Pediatrics of Sichuan University Affiliated Chengdu Second People's Hospital,a tertiary children's hospital in Chengdu,southwest China.Children aged<18 years who underwent MP-related laboratory testing between 1 January 2021 and 31 December 2025 were enrolled.All visits carried a timestamp;period boundaries were defined by calendar day(visits dated before 1 January 2023 were assigned to the NPI phase,and visits from 1 January 2023 to 31 December 2025 to the post-NPI phase),so that the phase and calendar-year strata are mutually consistent.Visits were de-duplicated by registration number and admission number,so that each visit contributed at most one record per testing stream.All eligible visits were included;no a priori sample-size calculation was performed,and no imputation was required because age,sex and season were complete for all visits.The study is reported in accordance with the STROBE recommendations for observational studies.

Laboratory testing and case definitions

The primary case definition relied on serology,which was the only assay available throughout the entire study period,thereby guaranteeing a method-consistent comparison between the NPI and post-NPI phases.Serology was performed with a particle-agglutination assay reporting a qualitative MP antibody(negative/weakly positive/positive)together with an antibody titre series(1:40 to 1:10240).A visit was classified as serology-defined MP-positive when the

qualitative antibody was positive or weakly positive,or when the 1:80(or higher)titre was positive or weakly positive.To quantify the influence of the positivity threshold we additionally applied a strong-positive-only definition(weakly positive results disregarded)and a stringent titre definition(positive only if the antibody titre reached≥1:160),and repeated the between-phase comparison under each definition.Two secondary assays were available only in the post-NPI era and were analysed separately rather than being used to redefine the primary outcome:(i)NAT,a fluorescence polymerase chain reaction(PCR)assay detecting MP and the macrolide-resistance mutations A2063G and/or A2064G in domain V of the 23S rRNA gene(from November 2023),the presence of either mutation defining MRMP;and(ii)a 13-respiratory-pathogen PCR panel(adenovirus,influenza A,bocavirus,rhinovirus,influenza A(H1N1)pdm09,seasonal H3N2,influenza B,respiratory syncytial virus A/B,parainfluenza virus,human coronavirus OC43/HKU1/NL63/229E,human metapneumovirus,Chlamydia pneumoniae and MP)performed from March 2023.Co-infection was defined as the detection of at least one non-MP pathogen on the same panel.As NAT and serology interrogate different biological windows,we quantified their agreement among visits tested by both assays.

Environmental data

Daily mean air-quality and meteorological data for Chengdu(air quality index[AQI],PM2.5,PM10,SO2,NO2,CO,O3,temperature,relative humidity and wind speed)were obtained from a merged local monitoring dataset covering 2013–2026 and aggregated to monthly means aligned with the monthly MP positivity series.The monthly series used in the analysis are provided in Additional file 1:Table S1.

Statistical analysis

Continuous variables are expressed as median(interquartile range,IQR);categorical variables as counts(percentages).Proportions are reported with Wilson 95%confidence intervals(CIs).MP positivity rates were compared between phases,years,seasons,age groups and disease categories using Pearson's chi-squared test,and the presence of a monotonic gradient across ordered age groups was tested with the Cochran–Armitage trend test.To estimate the independent association of the post-NPI phase with serology-defined MP positivity,we fitted multivariable logistic regression models adjusted for age group,sex and season(and,in a parallel model,for calendar year),reporting adjusted odds ratios(aORs)with 95%CIs;the post-NPI model was refitted under the strong-positive-only and stringent titre definitions to assess robustness.The non-linear relationship between age and the odds of MP

positivity was modelled with restricted cubic splines(RCS;four knots)in a logistic generalised linear model,with odds ratios referenced to age 5 years(school-entry age)and 95%CIs obtained by 500 bootstrap resamples.Agreement between serology and NAT was summarised by the overall agreement proportion,Cohen's kappa,positive and negative percentage agreement,and the proportion of serology-positive results among NAT-positive visits and of serology-negative results among NAT-negative visits.Pathogen–pathogen associations were summarised by the phi coefficient,and the odds ratio of MP co-infection with each other pathogen was estimated from 2×2 tables;for sparse tables a Haldane–Anscombe continuity correction(0.5)was applied and estimates were flagged as unstable.The association between monthly MP positivity and each environmental variable at lags of 0–3 months was assessed by Spearman correlation,with Benjamini–Hochberg false-discovery-rate(FDR)correction applied across all variable–lag tests(10 variables×4 lags=40 tests per series).Because the environmental and MP series share strong seasonal and secular trends,the analysis was repeated on first-differenced series to remove common trends,again with FDR correction,and the number of paired observations retained at each lag is reported.No other adjustment for multiple comparisons was applied.Two-sided $p<0.05$ was considered statistically significant.All analyses were performed in Python 3.13(statsmodels,SciPy,pandas).

Results

General characteristics of the study population

A total of 11,531 MP-tested visits by children aged<18 years were included across the 2021–2025 study period;4,295 visits(37.25%,95%CI 36.37–38.13)were serology-defined MP-positive(Table 1).The cohort was almost entirely composed of hospitalised children(99.91%).The MP positivity rate was significantly higher in the post-NPI phase(40.94%,2,254/5,506)than in the NPI phase(33.88%,2,041/6,025)($\chi^2=61.08$,$p<0.001$);after adjustment for age group,sex and season the difference remained significant(aOR 1.16,95%CI 1.07–1.26,$p<0.001$).MP positivity also differed significantly by sex(female 43.89%vs male 31.89%,$\chi^2=175.08$,$p<0.001$),age group($p<0.001$)and season($p<0.001$).The median age of MP-positive children was 4 years(IQR 3–7),higher than that of the overall tested population(3 years,IQR 1–6).

Epidemiological trend and seasonal variation of MP

Year by year,MP positivity was 36.34%(2021),31.37%(2022),34.87%(2023),52.30%(2024)and 38.01%(2025),peaking in

2024;relative to 2021,the adjusted odds of MP positivity were highest in 2024(aOR 1.44,95%CI 1.27–1.64)and,consistent with the initial suppression,lower in 2022(aOR 0.76,95%CI 0.67–0.85).The monthly MP positivity rate and testing volume are shown in Fig.1A.MP displayed pronounced seasonality,with the highest positivity in winter(43.23%)and autumn(42.11%),followed by summer(34.10%)and spring(31.41%)(χ^2=130.84,p<0.001)(Fig.1B).Stratified by phase,post-NPI positivity exceeded NPI positivity in every season(Fig.1C).Importantly,the monthly testing volume was not correlated with the monthly positivity rate(Spearmanρ=−0.06,p=0.66),arguing against a detection-intensity artefact driving the observed changes.

Age distribution of MP positivity

MP positivity increased steeply with age,reaching 3.97%in infants aged<1 year,32.94%at 1–2 years,42.10%at 3–5 years and 56.95%at 6–14 years,before decreasing to 50.35%at 15–17 years(χ^2=1,437.97,p<0.001;Cochran–Armitage trend test z=35.9,p<0.001)(Fig.2A).In both phases the age-dependent pattern was similar,although post-NPI positivity was consistently higher(Fig.2B).RCS analysis with age 5 years as the reference revealed a non-linear age–risk relationship,with the odds ratio relative to age 5 years peaking at 7.3 years in the NPI phase(OR at 8 years 1.25,95%CI 1.10–1.46)and 8.7 years in the post-NPI phase(OR at 8 years 1.50,95%CI 1.26–1.57)(Fig.2C).

Macrolide resistance of MP

Among 929 NAT-confirmed MP-positive children,752(80.95%,95%CI 78.30–83.34)carried the A2063G and/or A2064G mutation(MRMP)(Table 2,Fig.3A).Because NAT was introduced in November 2023,this estimate describes MRMP among children tested during the late post-NPI period.Resistance varied significantly by season(winter 86.65%,summer 79.05%,spring 78.10%,autumn 74.07%;p=0.006)(Fig.3B)but not by age group(p=0.452)(Fig.3C).The age-specific estimates for children aged<1 year(n=17)and 15–17 years(n=15)were based on small numbers and should be interpreted cautiously.

MP co-infection

In the 13-pathogen panel cohort(4,905 visits during 2023–2025),832 children were MP-positive,of whom 186(22.36%,95%CI 19.66–25.31)had at least one co-infecting pathogen(Table 3,Fig.4A).The co-infection rate did not differ significantly between seasons(p=0.091)(Fig.4B)but was strongly age-dependent,being highest in infants(50.00%at<1 year)and declining with age(32.91%at 1–2 years,25.40%at 3–5 years and

18.60%at 6–14 years)(p<0.001;Cochran–Armitage trend test z=−4.87,p<0.001)(Fig.4C).The most frequently co-detected pathogen was human rhinovirus(n=102),followed by respiratory syncytial virus(n=22),adenovirus(n=18),human metapneumovirus(n=15)and parainfluenza virus(n=14)(Table 3).

Interaction between MP and other respiratory pathogens

Correlation analysis of the 13 pathogens revealed largely negative inter-pathogen associations,with the expected strong positive co-circulation of influenza A subtypes(Fig.5A).MP was antagonistic with most other pathogens,with an odds ratio of co-infection below 1 for Chlamydia pneumoniae(0.12),respiratory syncytial virus(0.19),parainfluenza virus(0.22),human metapneumovirus(0.28),bocavirus(0.30),adenovirus(0.31),human coronavirus(0.41),rhinovirus(0.42)and influenza A(0.44);no antagonism was observed for influenza B(OR 1.64,p=0.248),and the estimate for seasonal H3N2 was close to unity(OR 0.98,p=1.00).The estimates for influenza A(H1N1)pdm09 and Chlamydia pneumoniae were based on sparse cells(including a zero co-detection cell for H1N1)and were therefore unstable;a Haldane–Anscombe correction was applied and these two estimates should be interpreted qualitatively(Fig.5B).

Disease distribution

Considering all tested children,the MP positivity rate did not differ significantly across disease categories(non-severe pneumonia 38.24%,severe pneumonia 37.81%,bronchitis 34.21%and upper respiratory tract infection 33.33%;p=0.140)(Fig.6A).However,within severe pneumonia the MP positivity rate was markedly higher in the post-NPI phase(45.14%)than in the NPI phase(30.31%)(χ^2=115.16,p<0.001),whereas the corresponding between-phase differences for non-severe pneumonia(38.99%vs 37.53%,p=0.310),bronchitis(32.96%vs 35.06%,p=0.568)and upper respiratory tract infection(29.63%vs 44.44%,p=0.683)were not significant(Fig.6B).

Agreement between serology and NAT and robustness of the phase comparison

Among 599 visits tested by both serology and NAT,the two assays agreed in only 48.1%of visits(Cohen'sκ=−0.148),indicating poor and even slightly inverse agreement(Table 4A).Serology-positive/NAT-negative discordance occurred in 205 visits and serology-negative/NAT-positive discordance in 106 visits;the positive percentage agreement was 54.9%and the negative percentage agreement 26.9%.Among NAT-positive visits,70.1%were

serology-positive,whereas among NAT-negative visits only 16.0%were serology-negative(that is,84.0%were serology-positive despite a negative NAT).This asymmetry indicates that a serology-based definition yields substantially more positives than NAT,plausibly because antibody may persist after pathogen clearance or reflect past exposure,whereas NAT detects only current infection.We therefore describe our primary outcome explicitly as serology-defined MP positivity throughout,rather than as MP infection.Because NAT was introduced only in November 2023,it was unavailable during the NPI phase and could not be used to derive an independent NAT-based phase comparison.We instead assessed the robustness of the phase difference to the serological definition(Table 4B):the post-NPI increase was directionally consistent under all definitions,and was in fact larger under the stringent titre(≥1:160)definition(positivity 9.49%in the NPI phase vs 24.23%post-NPI;aOR 2.72,95%CI 2.44–3.05,$p<0.001$),whereas excluding weakly positive results did not alter any estimate(no visit was positive on a weakly positive result alone).Absolute positivity,however,was strongly definition-dependent(37.25%under the primary definition vs 16.53%under the stringent titre definition),underscoring that reported MP positivity rates must be interpreted in the context of the assay and threshold used.

Environmental correlates of MP

The monthly MP positivity series(36 months,2023–2025)was correlated with 10 environmental variables at lags of 0–3 months(40 tests per series).In the level series,four variables retained significance after FDR correction:MP positivity was inversely correlated with SO2($\rho=-0.55$,$q=0.019$),AQI(lag 3 months,$\rho=-0.51$,$q=0.033$),O3($\rho=-0.46$,$q=0.045$)and wind speed($\rho=-0.45$,$q=0.045$);temperature($\rho=-0.39$,$q=0.083$)and relative humidity(lag 3 months,$\rho=+0.41$,$q=0.083$)did not reach significance after correction(Fig.7A,Table 5).Because these series share strong seasonal and secular trends,we repeated the analysis on first-differenced data(Fig.7B).After de-trending,all associations attenuated:no variable remained significant after FDR correction(all $q\geq0.51$),and the strongest remaining signals were a negative correlation with O3(lag 1 month,$\rho=-0.42$,$p=0.013$,$q=0.51$),a positive correlation with PM2.5($\rho=+0.35$,$p=0.038$,$q=0.59$)and a negative correlation with temperature($\rho=-0.33$,$p=0.052$,$q=0.59$);notably,the SO2(−0.55 to+0.18)and AQI(−0.51 to+0.27)associations reversed or vanished.These ecological findings indicate that the apparent environmental associations in the level series are largely explained by shared seasonality and long-term trend and cannot be interpreted causally.

Discussion

This study provides a five-year,method-consistent characterisation of MP positivity in hospitalised children in southwest China spanning the NPI and post-NPI eras,integrating macrolide resistance,co-infection and pathogen interactions,and appraising both the robustness of the positivity definition and the ecological correlates of MP.Building on earlier single-centre reports from the same region that focused on the early pandemic period[10],our analysis extends the observation window through the post-NPI rebound and adds multivariable adjustment,sensitivity analyses across case definitions and a de-trending appraisal of environmental associations.

The removal of NPIs was associated with a marked increase in MP activity.MP positivity rose from 33.88%during the NPI phase to 40.94%after relaxation(aOR 1.16)and peaked at 52.30%in 2024,consistent with the widely reported post-pandemic MP resurgence in China[7,9,13].Sustained NPI implementation plausibly reduced MP exposure and blunted herd immunity,the'immunity debt'hypothesis[8,14],such that the resumption of social mixing among susceptible school-aged children precipitated a rebound;comparable suppression and subsequent rebound have been described in other Chinese centres[15–17].Reassuringly,the monthly testing volume was not correlated with positivity,indicating that the between-phase difference was unlikely to be an artefact of changing test intensity.Absolute positivity rates should nevertheless be interpreted with care:MP serology in our centre is ordered selectively for children with a high clinical suspicion of MP infection,and the estimate is further dependent on the assay and threshold used.The direction of the NPI-versus-post-NPI difference,however,was robust across all serological definitions,which strengthens the conclusion that a genuine epidemiological shift occurred.

MP positivity exhibited strong seasonality,peaking in autumn and winter,and a clear school-age predominance with a risk nadir in infancy,in line with previous reports[11,16].The non-linear age–risk analysis,referenced to age 5 years,localised the maximum odds at approximately 7–9 years and quantified a 1.25-fold(NPI)to 1.50-fold(post-NPI)increase in odds at age 8 years relative to school entry,reflecting the combined effects of waning maternal immunity in early life and intensified cross-infection once children enter school.That post-NPI positivity exceeded NPI positivity in every age group and every season suggests a broad,system-wide increase rather than a shift confined to one subgroup.The disproportionate rise in MP positivity among children with severe pneumonia(30.31%to 45.14%)further

indicates that the rebound carried a substantial clinical burden,not merely a surveillance signal.

The macrolide-resistance burden in our cohort was very high(80.95%),consistent with reports that resistance in China frequently exceeds 80%[3,4,18]and with post-pandemic surveillance reporting rates of 87–98%in some centres[5,19].The persistence of such a high resistance burden poses a considerable challenge to empirical macrolide therapy,particularly in school-aged children,and reinforces the value of rapid resistance testing and antimicrobial stewardship[17].We deliberately do not report an annual resistance trend,because the annual denominators were highly unbalanced(NAT was available for only two months of 2023 and for a small number of children in 2025),and a trend estimate derived from such data would be unreliable.

MP co-infection occurred in 22.36%of MP-positive children and was strongly enriched in infants,a pattern consistent with immature immune defence and broader pathogen exposure in early life[20,21].The predominance of human rhinovirus among co-detected pathogens is clinically relevant given its association with wheezing and asthma exacerbation[22].The widespread antagonistic interactions between MP and other respiratory pathogens(OR<1 for the majority)support the concept of viral–bacterial interference,plausibly mediated by interferon responses,resource competition and superinfection exclusion[23,24],although the cross-sectional design cannot establish directionality.

The poor agreement between serology and NAT($\kappa=-0.148$)deserves emphasis.Although the two assays interrogate different biological windows[1],the near-absence of agreement,together with the finding that 84%of NAT-negative visits were nonetheless serology-positive,indicates that a serology-defined case definition substantially over-identifies MP relative to a molecular reference.This has two implications.First,the absolute positivity rates reported here,and in particular their comparability with NAT-based or PCR-screening cohorts[25],should be interpreted cautiously.Second,and more reassuringly,the between-phase difference was robust:restricting the definition to high antibody titres(≥1:160)not only preserved the direction of the NPI-versus-post-NPI increase but amplified it,implying that the temporal signal is not an artefact of low-titre or weakly positive results.Resistance and co-infection estimates,being derived from the post-NPI NAT and panel subsets,describe those tested populations rather than all MP infections.

The environmental analysis requires careful interpretation.In the level series,MP activity appeared inversely associated with SO2,AQI,O3 and wind speed.However,because these

variables share pronounced seasonal and secular trends with MP,we repeated the analysis on first-differenced series and applied FDR correction across all variable–lag tests.After de-trending,no association remained statistically robust;the SO2 and AQI signals reversed in sign,and the strongest remaining signals(O3,PM2.5 and temperature)did not survive multiple-testing correction.The inverse associations seen in the level series are therefore best explained by shared temporal structure rather than by acute exposure effects.This finding is consistent with the observation that,for MP,apparent air-pollution relationships are highly sensitive to study design and temporal adjustment[11,12],and it cautions against causal interpretation of single-city ecological correlations.Larger,multi-city designs with individual-level exposure assessment and confounder control will be required to resolve whether any environmental signal is genuine.

This study has several limitations.First,it was retrospective and single-centre,and the cohort was almost entirely composed of hospitalised children,which limits generalisability to outpatient or community settings.Second,the primary outcome is serology-defined MP positivity,and serology agreed poorly with NAT;the absolute rates reported here should not be equated with the true MP infection rate,and although the between-phase comparison was robust across definitions,it could not be verified with an independent NAT-based comparison because NAT was introduced only in the post-NPI era.Third,the 13-pathogen panel and macrolide-resistance testing were available only in the post-NPI era,precluding a direct NPI-versus-post-NPI comparison of co-infection and resistance,and the unbalanced annual denominators precluded reliable trend estimation.Fourth,only the A2063G and A2064G mutations were interrogated,which may underestimate the true resistance rate.Fifth,several subgroup estimates,notably resistance and co-infection in the youngest and oldest age bands,were based on small numbers.Finally,the environmental analysis is ecological,was based on monthly aggregated data over 36 months,and cannot establish causality.

Conclusions

The relaxation of NPIs was associated with a substantial increase in serology-defined MP positivity among hospitalised children in Chengdu,together with a persistently high macrolide-resistance burden and a considerable co-infection rate that was highest in infants.MP positivity was strongly age-and season-dependent.Absolute positivity estimates were highly sensitive to the serological threshold and to the assay used,whereas the direction of the post-NPI increase was robust across definitions.Apparent environmental associations

were largely attributable to shared seasonal and secular trends and should not be interpreted causally.These findings support continued post-pandemic MP surveillance and call for definition-aware reporting and prospective,multicentre confirmation.

List of abbreviations

ADV:adenovirus
aOR:adjusted odds ratio
AQI:air quality index
CAP:community-acquired pneumonia
CI:confidence interval
FDR:false discovery rate
HCoV:human coronavirus
HMPV:human metapneumovirus
HPIV:human parainfluenza virus
HRV:human rhinovirus
HRSV:human respiratory syncytial virus
IQR:interquartile range
MP: Mycoplasma pneumoniae
MRMP:macrolide-resistant Mycoplasma pneumoniae
NAT:nucleic-acid testing
NPI:non-pharmaceutical intervention
OR:odds ratio
PCR:polymerase chain reaction
RCS:restricted cubic spline
URTI:upper respiratory tract infection

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Sichuan University Affiliated Chengdu Second People's Hospital(approval no.2025030503303).The requirement for written informed consent was waived by the Institutional Review Board owing to the retrospective and anonymised nature of the data.The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified datasets and the analysis code that support the findings of this study are available from the corresponding author on reasonable request,subject to institutional data-sharing policies.The monthly series underlying Fig.7 and Table 5 is provided in Additional file 1:Table S1.

Competing interests

The authors declare that they have no competing interests.

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Authors'contributions

AC and YLZ conceived and designed the study.YLZ,PD,YHC,YP,HZ and SYZ contributed to data acquisition,curation and laboratory testing.ZC contributed to the statistical methodology and validation.AC performed the statistical analysis and,together with YLZ,wrote and critically revised the manuscript.All authors read and approved the final manuscript.

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Figure legends

Fig.1 Epidemiological trend and seasonal variation of MP positivity,2021–2025

(A)Monthly number of MP-tested children(bars,left axis)and monthly MP positivity rate(line,right axis);the shaded area denotes the NPI phase(2021–2022).(B)MP positivity rate by season;error bars indicate Wilson 95%CIs,and numbers inside the bars indicate the number of MP-tested children in each season.(C)MP positivity rate by season and phase.MP,Mycoplasma pneumoniae;NPI,non-pharmaceutical intervention;CI,confidence interval.

Fig.2 Age distribution of MP positivity and non-linear age–risk relationship

(A)MP positivity rate by age group;error bars indicate Wilson 95%CIs.The chi-squared and Cochran–Armitage trend test results are shown.(B)MP positivity rate by age group and phase.(C)Non-linear age–risk relationship estimated by restricted cubic spline logistic regression(four knots),with odds ratios referenced to age 5 years;shaded bands indicate 95%CIs obtained by 500 bootstrap resamples,and dotted vertical lines mark the age at maximum odds in each phase.MP,Mycoplasma pneumoniae;CI,confidence interval.

Fig.3 Macrolide resistance among NAT-confirmed MP-positive children

(A)Overall proportion of macrolide-resistant MP(MRMP)among NAT-confirmed MP-positive children;error bars indicate Wilson 95%CIs.(B)MRMP rate by season;numbers inside the bars indicate the number of NAT-confirmed MP-positive children tested in each season.(C)MRMP rate by age group;the estimates for children aged<1 year(n=17)and 15–17 years(n=15)are based on small numbers.MP,Mycoplasma pneumoniae;MRMP,macrolide-resistant Mycoplasma pneumoniae;NAT,nucleic-acid testing;CI,confidence interval.

Fig.4 Co-infection among MP-positive children,2023–2025

(A)Overall proportion of MP-positive children with at least one co-detected pathogen on the 13-pathogen panel.(B)Co-infection rate by season;numbers inside the bars indicate the number of MP-positive children in each season.(C)Co-infection rate by age group;numbers inside the bars indicate the number of MP-positive children in each group,and the estimate for children aged 15–17 years(0/9)is shown without a confidence interval because no co-detection occurred.All error bars indicate Wilson 95%CIs.MP,Mycoplasma pneumoniae;CI,confidence interval.

Fig.5 Interactions between MP and other respiratory pathogens

(A)Pairwise phi coefficients among the 13 respiratory pathogens detected by the panel;the diagonal is masked,and the colour scale is truncated at the maximum absolute off-diagonal coefficient.(B)Odds ratios of MP co-infection with each other pathogen(log scale),with 95%CIs;odds ratios below 1 indicate antagonism.Odds ratios and 95%CIs are annotated to the right of each row.(a)Haldane–Anscombe correction(0.5)was applied because of sparse cells,including a zero co-detection cell for influenza A(H1N1)pdm09;these estimates are unstable and should be interpreted qualitatively.MP,Mycoplasma pneumoniae;CI,confidence interval.

Fig.6 MP positivity by disease category and phase

(A)MP positivity rate by disease category among all tested children;numbers inside the bars indicate the number of children in each category.(B)MP positivity rate by disease category and phase;asterisks denote the significance of the between-phase comparison(***p<0.001;n.s.,not significant).URTI,upper respiratory tract infection;MP,Mycoplasma pneumoniae;NPI,non-pharmaceutical intervention.

Fig.7 Environmental correlates of monthly MP positivity before and after de-trending

(A)Spearman correlations between monthly MP positivity and each environmental variable at the lag(0–3 months)with the largest absolute coefficient,in the level series;asterisks denote associations surviving Benjamini–Hochberg false-discovery-rate correction($q<0.05$).(B)Corresponding correlations after first-differencing of both series to remove shared seasonal and secular trends;no association survived false-discovery-rate correction.Values beside each bar are Spearman rho.The monthly series(36 months,2023–2025)are provided in Additional file 1:Table S1.

Tables

Table 1 Characteristics of MP-tested children by phase and calendar year,2021–2025

Characteristic	N	MP-positive,n	MP-negative,n	Positivity,%(95%CI)
Overall	11,531	4,295	7,236	37.25(36.37–38.13)
NPI phase(2021–2022)	6,025	2,041	3,984	33.88(32.69–35.08)
Post-NPI phase(2023–2025)	5,506	2,254	3,252	40.94(39.65–42.24)
Year 2021	3,038	1,104	1,934	36.34(34.65–38.07)
Year 2022	2,987	937	2,050	31.37(29.73–33.06)
Year 2023	2,971	1,036	1,935	34.87(33.18–36.60)
Year 2024	1,780	931	849	52.30(49.98–54.62)
Year 2025	755	287	468	38.01(34.62–41.53)
Male	6,379	2,034	4,345	31.89(30.75–33.04)
Female	5,152	2,261	2,891	43.89(42.54–45.25)
Age<1 year	1,938	77	1,861	3.97(3.19–4.94)
Age 1–2 years	2,568	846	1,722	32.94(31.15–34.79)
Age 3–5 years	4,105	1,728	2,377	42.10(40.59–43.61)
Age 6–14 years	2,634	1,500	1,134	56.95(55.05–58.83)
Age 15–17 years	286	144	142	50.35(44.59–56.10)
Spring	3,499	1,099	2,400	31.41(29.89–32.97)
Summer	2,713	925	1,788	34.10(32.33–35.90)
Autumn	2,541	1,070	1,471	42.11(40.20–44.04)
Winter	2,778	1,201	1,577	43.23(41.40–45.08)

NPI,non-pharmaceutical intervention;MP,Mycoplasma pneumoniae;CI,confidence interval.Phase difference:χ^2=61.08,p<0.001;adjusted odds ratio(post-NPI vs NPI,adjusted for age group,sex and season)=1.16(95%CI 1.07–1.26),p<0.001.Sex:χ^2=175.07,p<0.001.Age group:χ^2=1438.0,p<0.001(Cochran–Armitage trend z=35.9,p<0.001).Season:χ^2=130.84,p<0.001.Year 2024 vs 2021:adjusted OR 1.44(95%CI 1.26–1.64).Median age:overall 3 years(IQR 1–6);MP-positive 4 years(IQR 3–7).99.91%of visits were inpatient.Phase and calendar-year strata are mutually consistent(NPI 6,025+post-NPI 5,506=11,531).

549 **Table 2 Macrolide resistance among NAT-confirmed MP-positive children**

Subgroup	MP-positive tested,n	MRMP,n	MRMP,%(95%CI)
Overall	929	752	80.95(78.30–83.34)
Spring	274	214	78.10(72.84–82.59)
Summer	210	166	79.05(73.05–84.01)
Autumn	108	80	74.07(65.08–81.41)
Winter	337	292	86.65(82.60–89.87)
Age<1 years	17	13	76.47(52.74–90.45)
Age 1-2 years	104	88	84.62(76.46–90.30)
Age 3-5 years	318	253	79.56(74.79–83.63)
Age 6-14 years	475	388	81.68(77.96–84.90)
Age 15-17 years	15	10	66.67(41.71–84.82)

550 NAT,nucleic-acid testing;MP,Mycoplasma pneumoniae;MRMP,macrolide-resistant Mycoplasma pneumoniae(A2063G and/or
551 A2064G mutation);CI,confidence interval.Resistance differed significantly by season(p=0.006)but not by age group(p=0.452).NAT
552 was available only from November 2023;an annual trend was not estimated because the annual denominators were highly
553 unbalanced.Estimates for children aged<1 year and 15–17 years are based on small numbers.

554

555 **Table 3 Co-detected pathogens among MP-positive children,2023–2025**

Co-detected pathogen	Co-detections,n	Odds ratio(95%CI)	p
Human rhinovirus	102	0.42(0.34–0.52)	<0.001
Respiratory syncytial virus	22	0.19(0.12–0.29)	<0.001
Adenovirus	18	0.31(0.19–0.50)	<0.001
Human metapneumovirus	15	0.28(0.16–0.46)	<0.001
Parainfluenza virus	14	0.21(0.13–0.37)	<0.001
Influenza A	12	0.44(0.24–0.79)	0.002
Human coronavirus	9	0.41(0.21–0.81)	0.004
Seasonal H3N2	8	0.98(0.47–2.05)	1.000
Influenza B	8	1.64(0.75–3.57)	0.248
Bocavirus	7	0.30(0.14–0.63)	<0.001
Chlamydia pneumoniae	2	0.12(0.03–0.41)a	<0.001
Influenza A(H1N1)pdm09	0	0.04(0.00–0.60)a	<0.001

556 MP,Mycoplasma pneumoniae;CI,confidence interval.Co-infection(at least one non-MP pathogen)was detected in 186 of 832 MP-
557 positive children(22.36%,95%CI 19.66–25.31;4,905 panel-tested visits).Odds ratios are for MP co-infection with the corresponding
558 pathogen;an odds ratio below 1 indicates antagonism.Counts exceed the number of co-infected children because of multiple co-
559 detections.a Haldane–Anscombe correction(0.5)was required for influenza A(H1N1)pdm09 and Chlamydia pneumoniae because of
560 sparse cells,including a zero co-detection cell for H1N1;these estimates are unstable and should be interpreted qualitatively.

561

Table 4 Serology–NAT agreement and sensitivity of the phase comparison

A.Cross-tabulation of serology and NAT among visits tested by both assays

Serology	NAT positive	NAT negative	Total
Positive	249	205	454
Negative	106	39	145
Total	355	244	599

Overall agreement 48.1%;Cohen'sκ=-0.148(poor agreement);positive percentage agreement 54.9%;negative percentage agreement 26.9%.Among NAT-positive visits,70.1%were serology-positive;among NAT-negative visits,only 16.0%were serology-negative.

B.Between-phase comparison under alternative serological positivity definitions

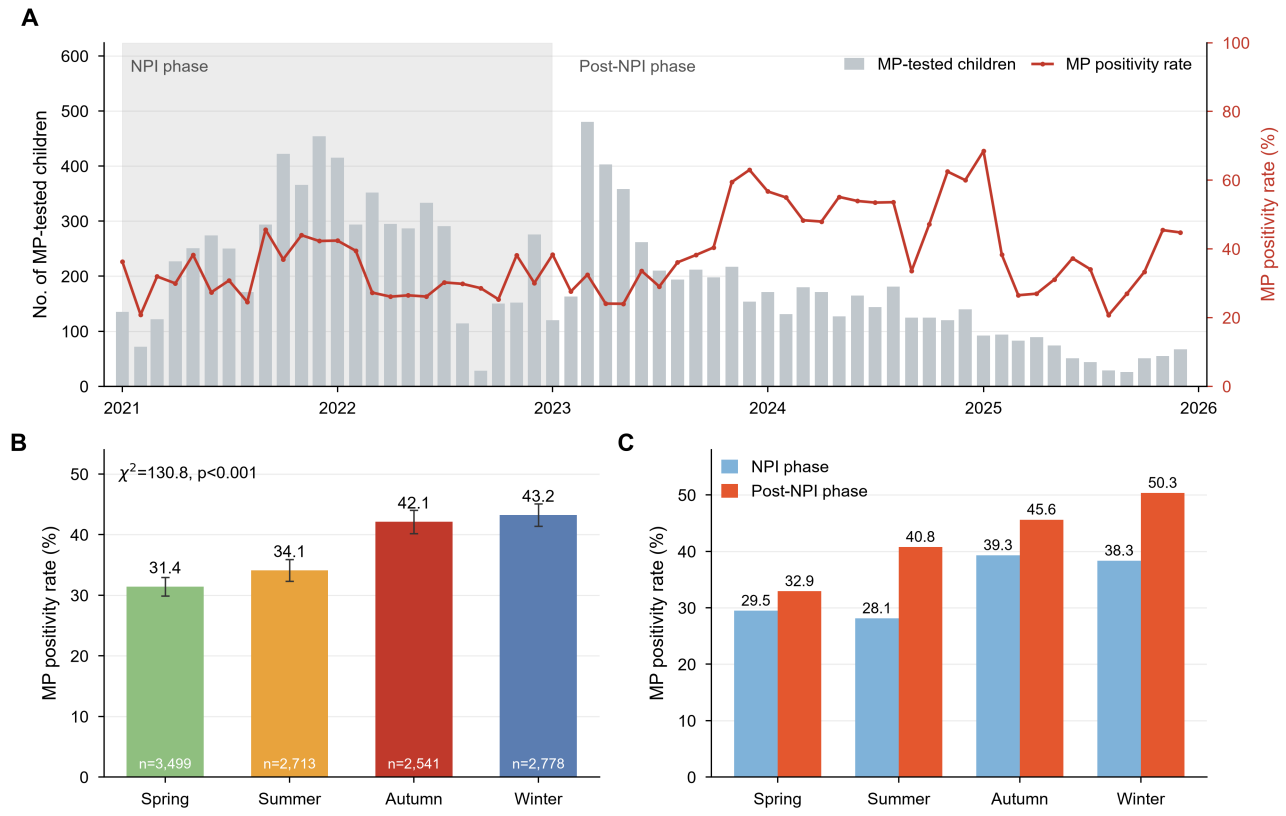
Definition	Overall positivity,%(95%CI)	NPI,%	Post-NPI,%	Adjusted OR(95%CI)
Primary(qualitative positive or weakly positive,or titre≥1:80)	37.25(36.37–38.13)	33.88	40.94	1.16(1.07–1.26)
Strong-positive only(weakly positive results excluded)	37.25(36.37–38.13)	33.88	40.94	1.16(1.07–1.26)
Stringent(positive only if titre≥1:160)	16.53(15.86–17.22)	9.49	24.23	2.72(2.44–3.05)

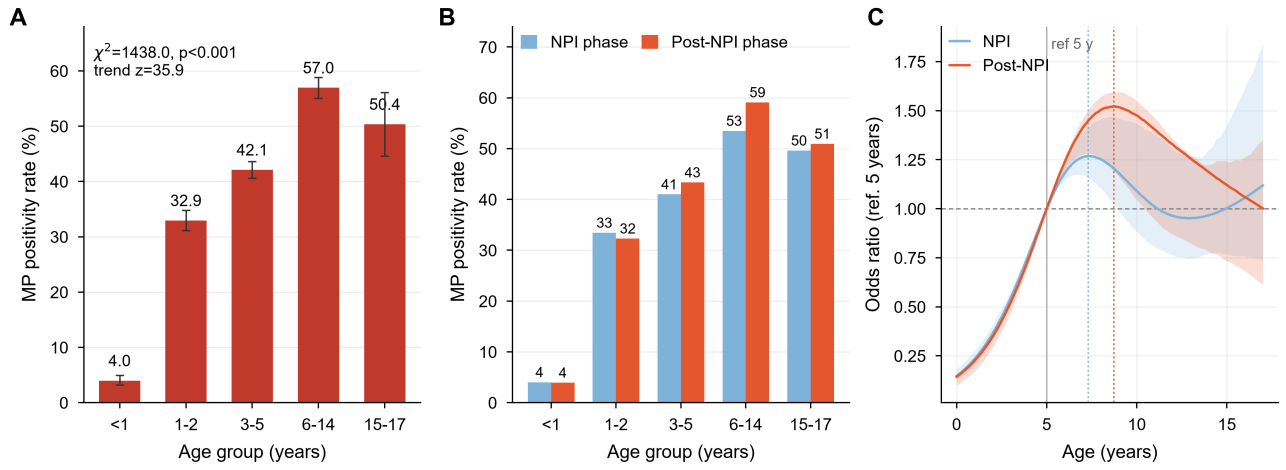
NAT,nucleic-acid testing;NPI,non-pharmaceutical intervention;CI,confidence interval;OR,odds ratio.Overall positivity is across the 2021–2025 serology cohort(n=11,531).Adjusted ORs(post-NPI vs NPI)are adjusted for age group,sex and season;all p<0.001.The strong-positive-only definition is identical to the primary definition because no visit was positive on a weakly positive result alone.

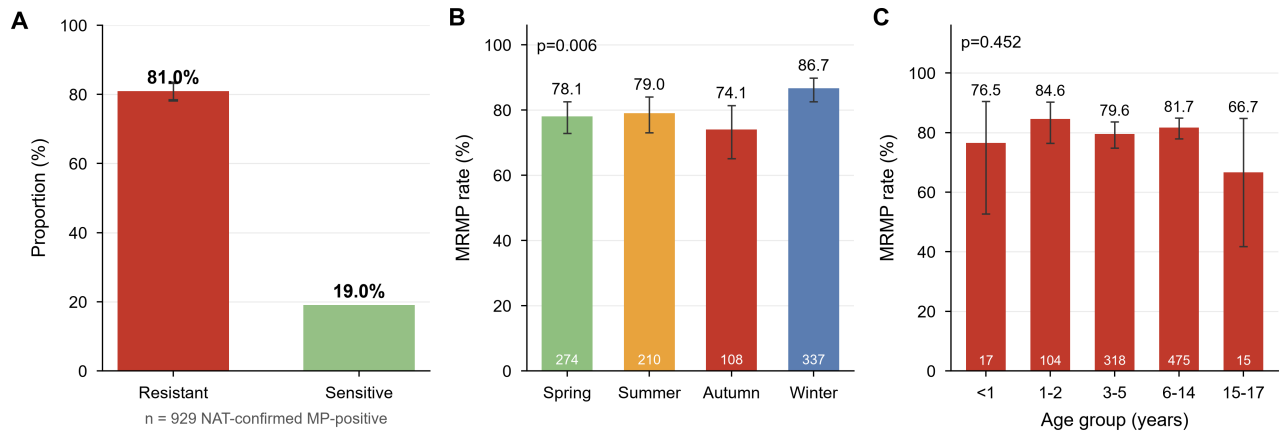
Table 5 Environmental correlates of monthly MP positivity,level and first-differenced series

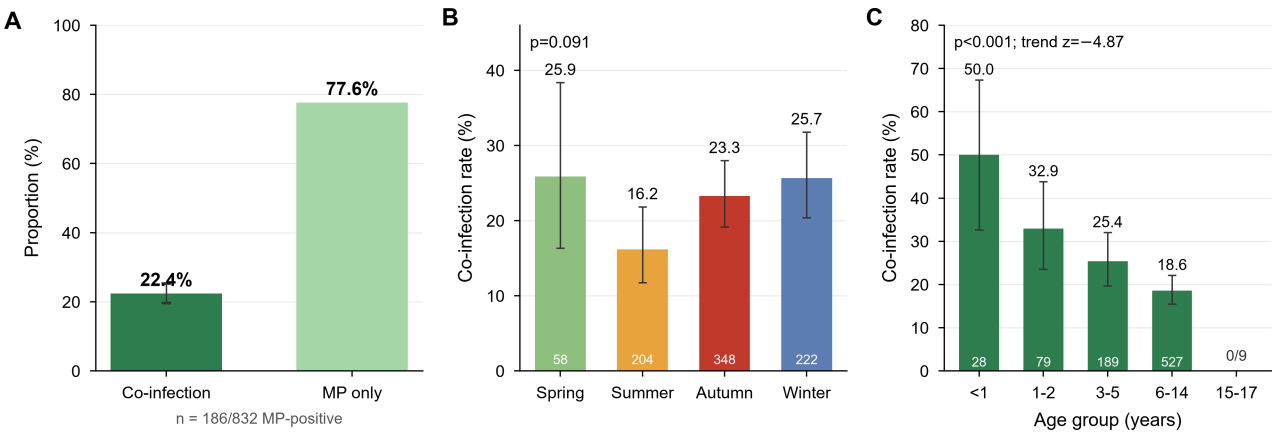
Variable	Levelρ(best lag)	p	q(FDR)	First-differencedρ(best lag)	p	q(FDR)
SO2	-0.55(lag 0)	<0.001	0.019	+0.18(lag 2)	0.309	0.652
AQI	-0.51(lag 3)	0.002	0.033	+0.27(lag 0)	0.113	0.588
O3	-0.46(lag 0)	0.005	0.045	-0.42(lag 1)	0.013	0.510
Wind speed	-0.45(lag 0)	0.006	0.045	-0.29(lag 0)	0.089	0.588
Relative humidity	+0.41(lag 3)	0.019	0.083	-0.28(lag 2)	0.114	0.588
Temperature	-0.39(lag 0)	0.017	0.083	-0.33(lag 0)	0.052	0.588
PM10	-0.34(lag 3)	0.056	0.175	+0.26(lag 0)	0.131	0.588
PM2.5	+0.34(lag 0)	0.046	0.175	+0.35(lag 0)	0.038	0.588
NO2	-0.32(lag 3)	0.070	0.192	+0.26(lag 1)	0.139	0.588
CO	+0.21(lag 0)	0.219	0.351	-0.26(lag 2)	0.141	0.588

MP,Mycoplasma pneumoniae;FDR,Benjamini–Hochberg false discovery rate;NA,not applicable.The monthly series covered 36 months(2023–2025).The best lag is the lag(0–3 months)with the largest absolute Spearman rho.FDR correction was applied across all 40 variable–lag tests in the level series and 40 tests in the first-differenced series.In the first-differenced series,the number of paired observations ranged from 33 to 35 across lags.No environmental association remained significant after de-trending and FDR correction.

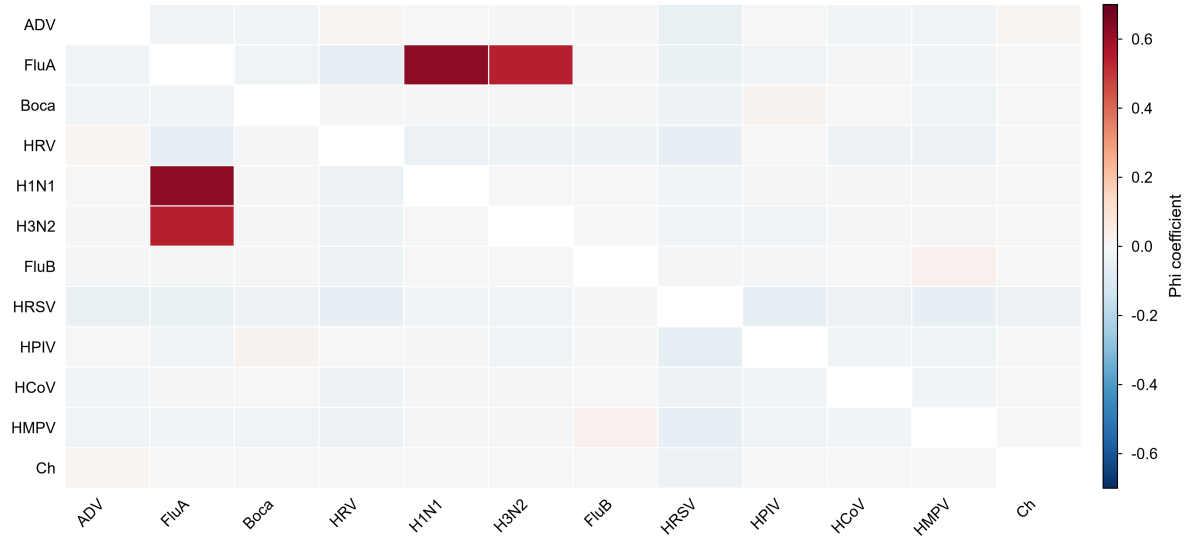

A
NPI phase
Post-NPI phase
MP-tested children
MP positivity rate
No. of MP-tested children
MP positivity rate (%)
0
100
200
300
400
500
600
0
20
40
60
80
100
2021
2022
2023
2024
2025
2026
B
χ^2=130.8, p<0.001
MP positivity rate (%)
31.4
34.1
42.1
43.2
n=3,499
n=2,713
n=2,541
n=2,778
Spring
Summer
Autumn
Winter
C
NPI phase
Post-NPI phase
MP positivity rate (%)
29.5
32.9
28.1
40.8
39.3
45.6
38.3
50.3
Spring
Summer
Autumn
Winter


A
χ^2=1438.0, p<0.001
trend z=35.9
MP positivity rate (%)
4.0
32.9
42.1
57.0
50.4
<1
1-2
3-5
6-14
15-17
Age group (years)
B
NPI phase
Post-NPI phase
MP positivity rate (%)
4
4
33
32
41
43
53
59
50
51
<1
1-2
3-5
6-14
15-17
Age group (years)
C
NPI
Post-NPI
ref 5 y
Odds ratio (ref. 5 years)
Age (years)

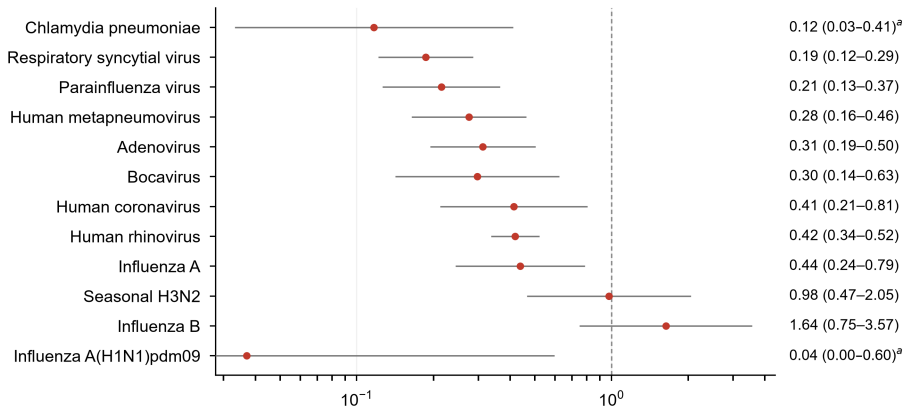

A
Proportion (%)
100
80
60
40
20
0
81.0%
19.0%
Resistant
Sensitive
n = 929 NAT-confirmed MP-positive
B
MRMP rate (%)
p=0.006
78.1
79.0
74.1
86.7
274
210
108
337
Spring
Summer
Autumn
Winter
C
MRMP rate (%)
p=0.452
76.5
84.6
79.6
81.7
66.7
17
104
318
475
15
<1
1-2
3-5
6-14
15-17
Age group (years)


A
Proportion (%)
100
80
60
40
20
0
22.4%
77.6%
Co-infection
MP only
n = 186/832 MP-positive
B
p=0.091
Co-infection rate (%)
40
30
20
10
0
25.9
16.2
23.3
25.7
58
204
348
222
Spring
Summer
Autumn
Winter
C
p<0.001; trend z=−4.87
Co-infection rate (%)
80
70
60
50
40
30
20
10
0
50.0
32.9
25.4
18.6
0/9
28
79
189
527
<1
1-2
3-5
6-14
15-17
Age group (years)

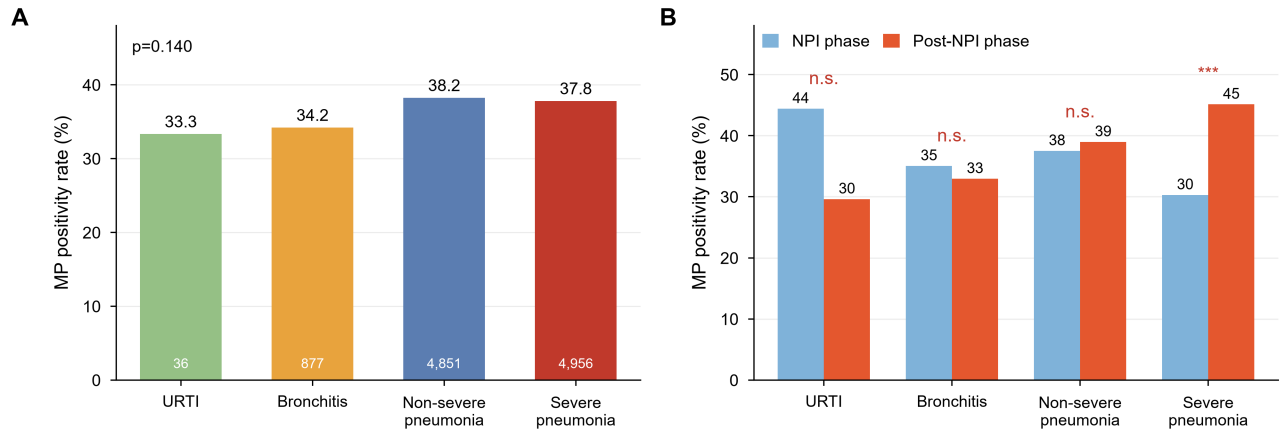
A

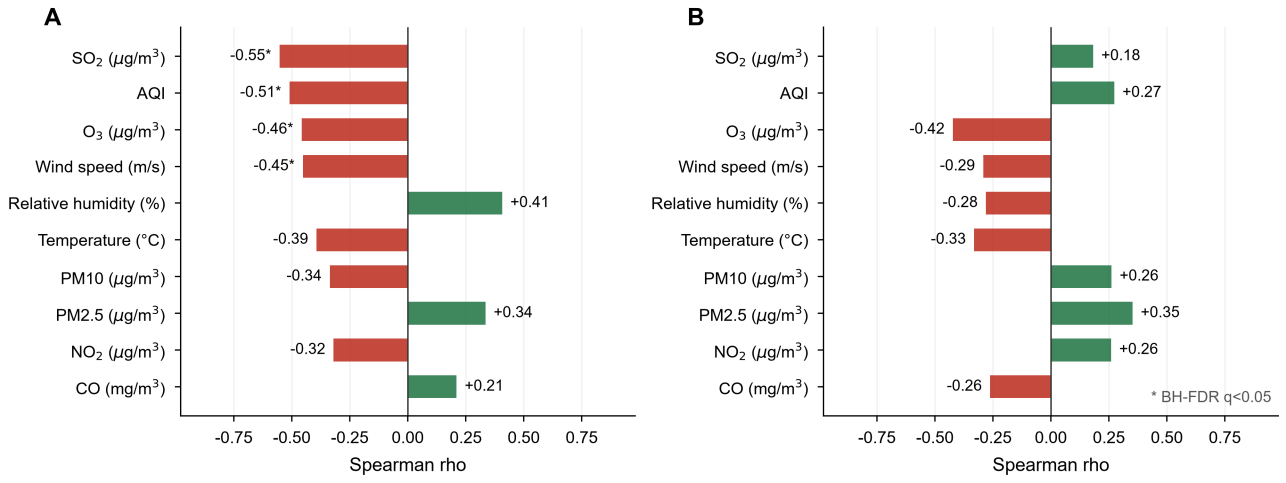


B



OR<1 indicates antagonism; [a]Haldane–Anscombe correction applied (sparse cells)


A
p=0.140
MP positivity rate (%)
0
10
20
30
40
33.3
34.2
38.2
37.8
36
877
4,851
4,956
URTI
Bronchitis
Non-severe pneumonia
Severe pneumonia
B
NPI phase
Post-NPI phase
MP positivity rate (%)
0
10
20
30
40
50
n.s.
n.s.
n.s.
***
44
30
35
33
38
39
30
45
URTI
Bronchitis
Non-severe pneumonia
Severe pneumonia


A
SO2 (μg/m3)
AQI
O3 (μg/m3)
Wind speed (m/s)
Relative humidity (%)
Temperature (°C)
PM10 (μg/m3)
PM2.5 (μg/m3)
NO2 (μg/m3)
CO (mg/m3)
-0.55*
-0.51*
-0.46*
-0.45*
+0.41
-0.39
-0.34
+0.34
-0.32
+0.21
-0.75 -0.50 -0.25 0.00 0.25 0.50 0.75
Spearman rho
B
SO2 (μg/m3)
AQI
O3 (μg/m3)
Wind speed (m/s)
Relative humidity (%)
Temperature (°C)
PM10 (μg/m3)
PM2.5 (μg/m3)
NO2 (μg/m3)
CO (mg/m3)
+0.18
+0.27
-0.42
-0.29
-0.28
-0.33
+0.26
+0.35
+0.26
-0.26
* BH-FDR q<0.05
-0.75 -0.50 -0.25 0.00 0.25 0.50 0.75
Spearman rho

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