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Original Article

The epidemiology, clinical characteristics, and macrolide susceptibility of *Mycoplasma pneumoniae* pneumonia in children in Southern Taiwan, 2019–2020

Cheng-Yen Kuo [a], Wei-Chun Tsai [b], Hui-Feng Lee [a], Tzong-Shiann Ho [b], Li-Min Huang [c], Ching-Fen Shen [a,e,], Ching-Chuan Liu [a,d,*] On behalf of Taiwan Pediatric Infectious Disease Alliance (TPIDA)**

[a] *Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan City, Taiwan*
[b] *Department of Emergency Medicine, Chi Mei Medical Center, Tainan City, Taiwan*
[c] *Department of Pediatrics, National Taiwan University and Hospital, Taipei City, Taiwan*
[d] *Center of Infectious Disease and Signaling Research, National Cheng Kung University, Tainan City, Taiwan*
[e] *Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

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KEYWORDS
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Abstract *Background:* Since the global use of the pneumococcal conjugate vaccine, *Mycoplasma pneumoniae* (MP) has become the most common bacterial cause of lower respiratory tract infections among children. Monitoring the changing epidemiology and antimicrobial resistance rates of this organism is important for MP clinical management.
Methods: This study characterizes key features of MP during the 2019–2020 epidemic in children in Taiwan. The cohort included all hospitalized children under 18 years of age with polymerase chain reaction (PCR)-confirmed community-acquired mycoplasma pneumonia (CAMP) in southern Taiwan. Macrolide resistance was identified by mutations in domain V of MP 23S rRNA. Severe disease referred to symptoms warranting oxygen therapy, septic shock, or intensive care unit admission.

* Corresponding author. Division of Pediatric Infectious Diseases, Department of Pediatrics, National Cheng Kung University Hospital, No.138, Sheng-Li Road, North District, Tainan City, 70403, Taiwan. Fax: +886 6 2753083.
** Corresponding author. Division of Pediatric Infectious Diseases, Department of Pediatrics, National Cheng Kung University Hospital, No.138, Sheng-Li Road, North District, Tainan City, 70403, Taiwan. Fax: +886 6 2753083.
E-mail addresses: drshen1112@gmail.com (C.-F. Shen), liucc@mail.ncku.edu.tw (C.-C. Liu).

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Results: Among 495 LRTI patients, 195 (39.4%) had CAMP, of which 106 (54.4%) had concurrent serological evidence of MP infection. The diagnostic sensitivity of IgM in the acute phase was 65.6%. CAMP case numbers were highest from July 2019 to January 2020. The most common clinical presentations of CAMP were fever (99.0%), cough (99.0%), and coryza (31.8%). Despite a high rate of macrolide resistance (88.1%), macrolide-resistant MP (MRMP) did not differ from macrolide-sensitive MP (MSMP) in clinical course or severity. Delayed administration of effective antimicrobial treatment was also associated with severe disease ($p < 0.05$).
Conclusion: Early diagnosis and determination of MRMP are needed for effective management of MP infection.

Introduction

After widespread use of the pneumococcal conjugate vaccine, *Mycoplasma pneumoniae* (MP) has become the leading cause of community-acquired pneumonia in children.[1] Although school-age children account for the majority of pediatric community-acquired mycoplasma pneumonia (CAMP), younger children are also vulnerable to MP infection and have more severe diseases.[2] While most CAMP cases presented as mild illness, 0.5—2% patients experienced fatal pulmonary complications such as organizing pneumonia, chronic interstitial fibrosis, and acute respiratory distress syndrome.[3,4] MP infection can also cause extrapulmonary symptoms, including neurological, dermatological, hematological, cardiovascular, musculoskeletal, or renal involvement that may result in long-term sequelae. Greater risk for severe MP infections are raised in young healthy male adults, children under 5 years of age, and those with delayed or no appropriate antimicrobial treatment.[5]

Polymerase chain reaction (PCR) assay, the gold standard for MP detection, is not always available in all clinical settings. Instead, serological assay remains the most common diagnostic method because of its low cost, convenience, and universality.[6] The poor sensitivity of serological tests in acute phase infections may delay or misguide appropriate antimicrobial treatment of suspected MP infections.[7] Macrolides are the first-line antimicrobial agents used for treating MP infection. However, the worldwide increase in macrolide-resistant MP (MRMP) since 2000 poses a threat to MP infection management.[5,8—12] In Taiwan, the prevalence of MRMP has dramatically increased from 12% to 77% recently, and MRMP-related treatment failure was also observed.[5,9,11,13,14] Although a recent meta-analysis revealed no association between macrolide resistance and disease severity, MRMP contributed to longer fever duration, hospital stays, and antibiotic drug course.[14]

This study used clinical data from MP patients during the 2019—2020 epidemic to explore the diagnostic value of serological tests, to compare MP characteristics with those of a previous nationwide study of pediatric community-acquired pneumonia, and to identify changes in the clinical epidemiology of MP over time. Macrolide resistance and its association with clinical manifestations and disease severity were also investigated.

Materials and methods

Taiwan Pediatric Infectious Disease Alliance

This study is part of the joint MRMP project in Taiwan conducted by the Taiwan Pediatric Infectious Disease Alliance (TPIDA), a collaborative consortium of nine pediatric infectious disease departments in tertiary medical centers.[15] This study was approved by the Institutional Review Board (approval number: A-BR-107-053) of all participating hospitals. Informed consents/assents were obtained from each participating patient or the patient's guardian.

Patients and data collection

We prospectively recruited hospitalized children age under 18 with PCR-confirmed MP-related lower respiratory tract infection (LRTIs) diagnosed at National Cheng Kung University Hospital (NCKUH) from May 2019 to May 2020. NCKUH is a 1200-bed tertiary care university hospital located in Tainan, southern Taiwan. Patients' demographic information, medical history, clinical characteristics, laboratory findings, radiological findings, and treatment outcomes were retrieved from medical records. Participants were excluded if they were immunocompromised, bedridden, or ventilator-dependent before the current illness to avoid analytic bias regarding disease severity. We also retrieved the case numbers of all hospitalized children aged under 18 in NCKUH from 2011 to 2020 with the diagnosis of pneumonia due to MP (ICD10 code J157) infection to examine the epidemiological trends in the past 10 years.

Microbiological investigation

Respiratory specimens (nasopharyngeal swab, sputum, bronchial lavage fluid, or pleural effusion) for virus isolation and blood samples for bacterial culture were collected from each patient. Other tests for infectious pathogens included sputum cultures, *Streptococcus pneumoniae* urine

antigen test (BinaxNOW, Abbott, Chicago, IL, USA), direct fluorescent-antibody assay for influenza A virus, influenza B virus, adenovirus, and respiratory syncytial virus (D 3 Ultra 8 DFA Respiratory Virus Screening & Identification Kit, Quidel, San Diego, CA, USA), or BioFire FilmArray Respiratory Panel (bioMérieux, Marcy-l'Étoile, France).

Throat swabs were obtained for MP PCR using loop-mediated isothermal amplification (LAMP) assay (HiberGene, Dublin, Ireland). MP serology tests included MP IgG measured by gelatin particle agglutination test kit (SERODIA-MYCO II, Fujirebio, Tokyo, Japan) in microtiter plates, and/or MP IgM by rapid immunochromatographic test (Biocard*Mycoplasma pneumoniae* IgM, ANIBiotech, Vantaa, Finland). All MP PCR-positive specimens were confirmed by genotyping of the 23S ribosomal RNA gene using a nested PCR assay (forward primer, 5′-GCA GTG AAG AAC GAG GGG-3'; reverse primer, 5′-CAC ACT TAG ATG CTT TCA GCG-3' [1758—2769 nucleotides] and forward primer, 5′-ACT ATA ACG GTC CTA AGG TA-3'; reverse primer, 5′-GTC CTC GCT TCG GTC CTC TCG-3' [1937—2684 nucleotides]) and DNA sequencing. Generally, macrolide resistance in the MP species is defined by mutations in the ribosomal target of the antibiotic, i.e., the 23S rRNA and the ribosomal proteins L4 and L22.[16] Here, in present study, we identified the macrolide resistance by DNA sequencing of the MP PCR product. Macrolide resistance was identified by the two common mutations, 2063 or 2064 in domain V of 23S rRNA.

Definitions

CAMP was defined as lower respiratory tract infection with radiological evidence of bronchopneumonia/lobar pneumonia and positive MP PCR from any respiratory specimen. Chest radiographs were interpreted by two pediatricians with no knowledge of the patient data. Extrapulmonary manifestations included central nervous system involvement (encephalopathy or pleocytosis in CSF analysis), elevated liver enzymes (above 80 U/L for aspartate transaminase or alanine transaminase), and dermatological involvement. Severe MP infection was defined as severe respiratory symptoms warranting oxygen therapy (with or without assisted ventilation), septic shock, or the need for intensive care. Effective treatment referred to macrolide for macrolide-sensitive MP (MSMP) patients or fluroquinolone or tetracycline for all patients. Delayed effective treatment referred to the lack of appropriate treatment within 5 days (<120 h) after fever onset.

Statistical analysis

All statistical analyses were performed using commercially available statistical software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Data are presented as percentages for qualitative data and means with standard deviations for quantitative data. Continuous data were analyzed using Student's *t*-test; categorical data were compared using the Fisher's exact test. All tests were two-tailed. Statistical significance was defined as $p < 0.05$ for all tests.

Results

Clinical characteristics

Of the 495 hospitalized patients with LRTIs, 203 were PCR-positive for MP. A total of 195 patients were enrolled after excluding 8 patients (3 immunocompromised, 2 bedridden, 3 ventilator-dependent) (Fig. 1A). Systemic underlying disease was present in 25 patients (12.8%), including asthma (n = 11; 5.6%), prematurity (n = 3; 1.5%), bronchopulmonary dysplasia (n = 3; 1.5%), neurological disorders (n = 5; 2.6%), chronic kidney disease (n = 3; 1.5%), and congenital heart disease (n = 3; 1.5%). The monthly distribution of all patients with LRTIs and MP infections is shown in Fig. 2. The number of patients in each group peaked from July 2019 to January 2020, and MP infections accounted for approximate 35—55% of the monthly LRTI patients.

All patients fulfilled the criteria for CAMP, including 100 (51.3%) with lobar pneumonia and 95 (48.7%) with bronchopneumonia (Table 1). The most common symptoms were fever (99.0%) and cough (99.0%), followed by coryza (31.8%), dyspnea (27.7%), and diarrhea (15.9%). Extrapulmonary manifestations occurred in 27 patients (13.8%), including generalized skin rash (11.8%), elevated liver enzymes (2.6%), and CNS involvement (1.0%). The coinfection rate was 5.6%, and the other causative agents included parainfluenza virus (n = 3), adenovirus (n = 3), respiratory syncytial virus (n = 3), and influenza virus type A (n = 1). The total ICU admission rate among the cohort was 4.1% (n = 8). Septic shock was the primary cause of ICU admission (n = 4; 50%), followed by oxygen need (n = 3; 37.5%), encephalopathy (n = 1; 12.5%), and erythema multiforme major (n = 1; 12.5%).

A MP outbreak was observed in the pediatric population of southern Taiwan in 2019—2020. The median annual hospitalized pediatric cases with the diagnosis of MP pneumonia from 2011 to 2020 was 26 (range 0—267), with spiked 267 in 2019 (Fig. 3).

Serological response in acute MP infection

The serologic indicators of the cohort during the acute and convalescent stages are shown in Fig. 1. Briefly, 106 patients (54.4%) had serological evidence of acute MP infection with at least one of the following: MP IgM conversion (32; 16.4%), four-fold or greater increase of MP IgG (67; 34.4%), or MP IgG >1:640 (100; 51.3%). Of these patients, 26 (13.3%) fulfilled all 3 criteria, and 39 (20%) met only one (Fig. 1B). Eighty-nine (45.6%) patients lacked complete serological survey. Three of the 89 patients had paired IgM results within one week and failed to seroconvert in the second serum samples.

Subgroup analysis by severity and macrolide resistance

The demographic and clinical characteristics of the patient cohort according to disease severity and macrolide

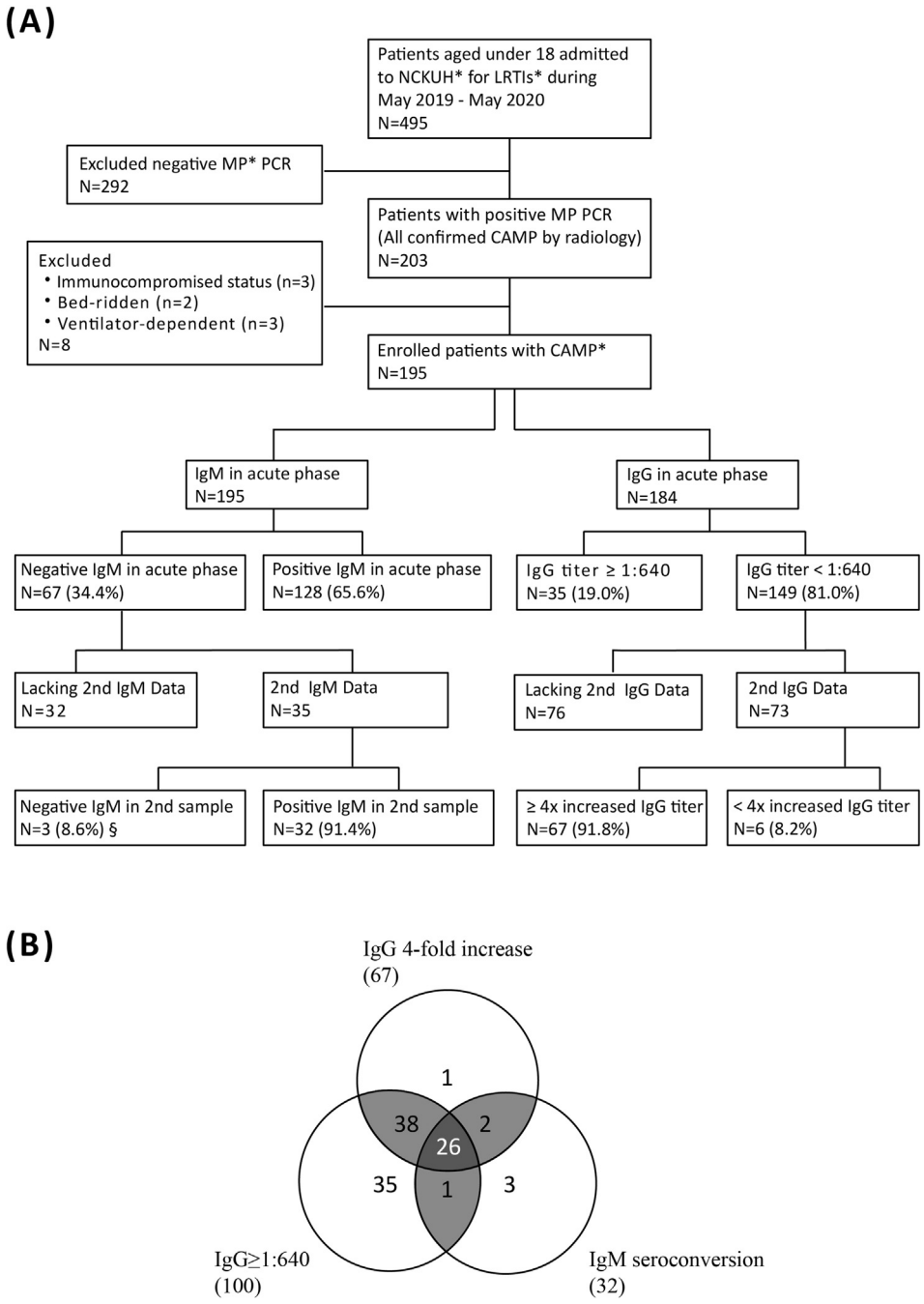

Figure 1. Workflow for MP infection identification and corresponding serological investigation. (A) Flowchart for distinguishing MP infection LRTI. (B) Venn diagram shows the patients with serological evidence of MP infection. A total of 106 patients had at least one of the criteria mentioned above. Abbreviations: CAMP, community acquired *Mycoplasma pneumoniae* pneumonia; LRTIs, lower respiratory tract infections; MP, *Mycoplasma pneumoniae*; NCKUH, National Cheng Kung University Hospital. §The time between consecutive IgM tests in these 3 patients was <7 days.

susceptibility are shown in Table 1. A total of 36 patients (18.5%) had severe CAMP, with 32 (16.4%) needing oxygen supplementation, and 8 (4.1%) receiving intensive care. Children age under 5, male sex, dyspnea, leukocytosis, and bronchopneumonia were significantly associated with severe CAMP (all $p < 0.05$). No differences were observed in underlying diseases, extrapulmonary manifestations, and the level of peak C-reactive protein (CRP).

A macrolide-resistant mutation in domain V of the MP 23S rRNA gene was present in 88.1% of the sequence-detectable samples (n = 159). The most frequent mutation was A2063G (n = 93; 66.4%), followed by A2063T (n = 46; 32.9%) and A2064G (n = 1; 0.7%). The MRMP group had more dyspnea ($p = 0.026$) and less coryza ($p = 0.008$) than did the MSMP group (Table 1). Before presenting to our hospital, 2 patients in the MSMP group (10.5%) received previous macrolide

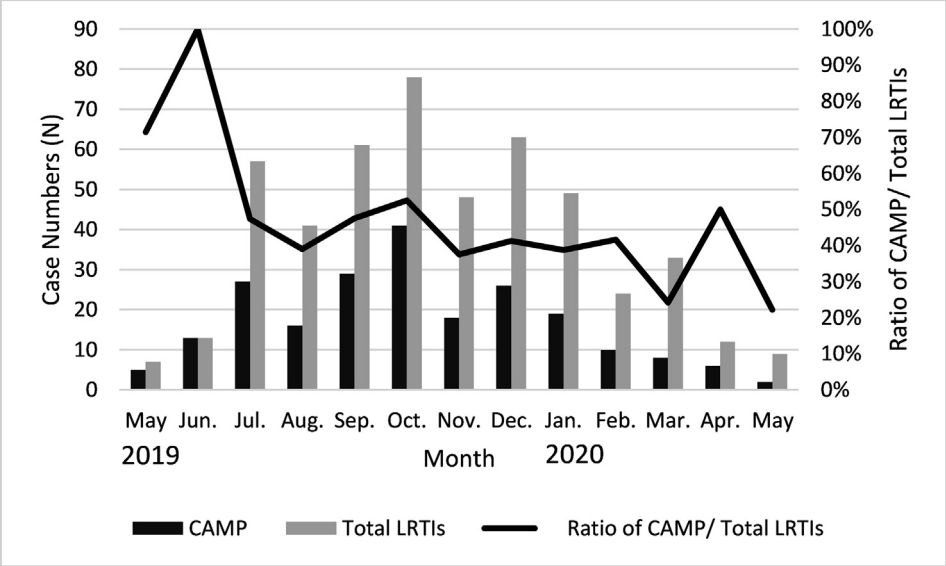

Figure 2. Monthly distribution of patients with CAMP and LRTIs in May 2019–May 2020. Abbreviations: CAMP: community acquired *Mycoplasma pneumoniae* pneumonia; LRTIs: lower respiratory tract infections.

treatment, significantly fewer than the 53 patients (37.8%) in the MRMP group ($p = 0.020$). All patients in the MSMP group received effective antimicrobial therapy. In contrast, only 80.7% of those in the MRMP group received effective antimicrobial therapy ($p < 0.05$). In the MRMP group, the duration of fever after admission was significantly shorter in the 113 patients treated with doxycycline (1.7 ± 1.5 days) than in the 27 patients not treated with doxycycline (2.3 ± 0.8 days) ($p = 0.034$). This delay in effective treatment was associated with significantly greater disease severity ($p < 0.05$) and with longer hospital stays and a higher prevalence of the need for oxygen supplementation (Table 2).

Discussion

We observed a surge in MP infections among pediatric LRTIs above the baseline threshold over a 12-month period during 2019–2020, indicating a local outbreak of MP infection. Compared to the study cohort of the previous epidemic, patients with CAMP had significantly lower ICU admission rates, less need for oxygen supplementation, and fewer hospital stays.[15] In contrast to other studies, MRMP was not associated with longer febrile periods, prolonged disease course, or longer hospital stays.[5,9,13,14]

MP infection accounts for 2–35% of LRTIs, with 18% of CAMP patients requiring hospitalization.[3,17–19] Previous studies reported that MP epidemics occur every three to seven years, with each episode lasting longer than 1 year.[18,20–22] Although MP infection occurs throughout the year, the peak is usually at the end of summer to early winter.[18,19,23] Our study confirmed this seasonality, with the peak case numbers occurring between July 2019 and January 2020. However, the number of cases of CAMP and LRTI both decreased sharply after February 2020. In addition to the natural seasonal distribution of MP, this decrease may have resulted from the national infection control policy instated due to the SARS-CoV-2 pandemic.

Although IgM is widely used for diagnosing acute MP infection, our study revealed that the sensitivity of IgM for acute stage diagnosis was only 65.6% (128/195), which is comparable to that reported previously.[6] In addition, IgM may persist with low titers for up to several years after acute infection.[24] MP PCR has become the gold standard for diagnosing acute MP infection for its high sensitivity and short turnaround time and has replaced serological testing in some clinical settings.[6,7,18] Nevertheless, the high sensitivity of PCR may give false results due to contamination in the respiratory tract. Meyer et al. recently developed an ELISpot assay-based IgM-antibody–secreting cell measurement for acute MP infection; this assay might avoid the shortcomings of conventional IgM testing and the potential diagnostic limitations of PCR.[25]

Macrolide resistance in MP infection is increasing worldwide, and the situation is especially severe in Asian countries.[11,26] A previous study in Taiwan reported a macrolide resistance rate of 12–77% among MP infections.[5,9,11,13] In our cohort, the rate of macrolide resistance was 88%, the highest rate reported in Taiwan. With increasing resistance, the use of macrolides as first-line antimicrobial therapy might result in more treatment failures and clinical course complications. A retrospective study showed that a delay in effective medication for MRMP was associated with a longer febrile period, a higher prevalence of severe disease, and higher CRP levels.[5] A systematic review of pooled data showed that compared with MSMP, MRMP had a longer febrile period, length of hospital stays, antibiotic treatment course, and defervescence time after macrolide treatment.[14] In our study, we observed no significant differences between the two groups with respect to disease severity or any clinical feature. A possible explanation for this observation is that most patients in our cohort were referred from local clinics that had already administered macrolide therapy; with awareness of the rising macrolide resistance rate, the doctors in

Table 1 Demographic and clinical characteristics of CAMP according to disease severity and macrolide resistance.

	Total (N = 195)	Non-Severe (N = 159; 81.5%)	Severe (N = 36; 18.5%)	*p*	MRMP (N = 140; 88.1%)	MSMP (N = 19; 11.9%)	*p*
Age (y)	6.6 ± 3.8	6.8 ± 3.6	5.8 ± 4.5	0.180	6.6 ± 3.4	8.0 ± 4.0	0.091
<5 years (n, [%])	75 (38.5)	55 (34.6)	20 (55.6)	**0.023***	50 (35.7)	5 (26.3)	0.608
Sex, male (n, [%])	98 (50.3)	68 (42.8)	30 (83.3)	**<0.001***	68 (48.6)	7 (36.8)	0.464
Underlying diseases (n, [%])	39 (20)	28 (17.6)	11 (30.6)	0.105	27 (19.3)	6 (31.6)	0.232
Symptoms							
Fever (n, [%])	193 (99.0)	158 (99.4)	35 (97.2)	0.336	139 (99.3)	19 (100)	>0.99
Cough (n, [%])	193 (99.0)	159 (100)	34 (94.4)	**0.033***	139 (99.3)	19 (100)	>0.99
Dyspnea (n, [%])	54 (27.7)	29 (18.2)	25 (69.4)	**<0.001***	41 (29.3)	1 (5.3)	**0.026***
Vomiting[a] (n, [%])	23 (11.8)	18 (11.3)	5 (13.9)	0.774	14 (10)	3 (15.8)	0.432
Diarrhea (n, [%])	31 (15.9)	26 (16.4)	5 (13.9)	0.806	26 (18.6)	1 (5.3)	0.201
Coryza (n, [%])	62 (31.8)	50 (31.4)	12 (33.3)	0.844	30 (21.4)	10 (52.6)	**0.008***
Extrapulmonary manifestations[b] (n, [%])	27 (13.8)	21 (13.2)	6 (16.7)	0.596	17 (12.1)	2 (10.5)	>0.99
Laboratory Data							
Leukocytosis[c] (n, [%])	24 (12.3)	15 (9.4)	9 (25)	**0.021***	14 (10)	1 (5.3)	>0.99
Highest CRP (mg/dL)	47.3 ± 50.8	45.9 ± 47.4	53.4 ± 63.9	0.513	46.7 ± 50.8	61.9 ± 50.3	0.224
Coinfection (n, [%])	11 (5.6)	9 (5.7)	2 (5.6)	>0.99	5 (3.6)	0	>0.99
Clinical course							
Duration of fever (d)	7.9 ± 3.5	8.0 ± 3.5	7.4 ± 3.4	0.348	8.1 ± 2.9	9.5 ± 4.7	0.08
Hospital Stays (d)	4.9 ± 4.7	4.4 ± 2.0	7.4 ± 9.9	**0.080***	5.0 ± 5.3	4.7 ± 2.0	0.805
ICU admission (n, [%])	8 (4.1)	0	8 (22.2)	**<0.001***	3 (2.1)	0 (0)	>0.99
O2 requirement (n, [%])	32 (16.4)	0	32 (88.9)	**<0.001***	25 (17.9)	1 (5.3)	0.317
Severe disease					26 (18.6)	1 (5.3)	0.201
Without effective Abx (n, [%])	27/159 (17.0)	23/132 (17.4)	4/27 (14.8)	>0.99	27 (19.3)	0 (0)	**0.045***
Chest X Ray							
Lobar pneumonia (n, [%])	100 (51.3)	88 (55.3)	12 (33.3)	**0.026***	86 (61.4)	9 (47.4)	0.319
Bronchopneumonia (n, [%])	95 (48.7)	71 (46.7)	24 (66.6)	**0.026***	54 (38.6)	10 (52.6)	0.319
Pleural effusion (n, [%])	8 (4.1)	7 (4.4)	1 (2.7)	>0.99	7 (5)	1 (5.3)	>0.99

[a] Vomiting refers to non-post-tussive vomiting.
[b] Including generalized skin rashes (11.8%), elevated liver enzymes (2.6%), and CNS involvement (1.0%).
[c] For age <5 years old, white blood cell count >15 000/μL; For age >5 years old, white blood cell count >11000/μL.
Data are shown as the mean ± standard deviation or number/tested number (percentage).
**p* values in bold font indicate statistical significance.
Abbreviations: d, days; CRP, C-reactive protein; OPD, outpatient department; Abx, antibiotics; Tx, treatment.

our institute tend to choose doxycycline as rescue therapy. Compared to 42% in northern Taiwan, 80.7% of our MRMP patients received effective antimicrobial therapy, primarily doxycycline.[5] With early administration of effective antimicrobial therapy, MRMP patients were treated as effectively as MSMP patients; therefore, no clinical differences were observed between these two groups. In Taiwan, the most common point mutation conferring macrolide resistance in MP is A2063G.[9,13] A2063G also was the major resistance mutation in our cohort. Clearly, the clinical severity or presentation of MP infection is not associated with macrolide resistance itself but rather correlates with delayed administration of effective antibiotics.

We compared primary data of 127 CAMP cases from a previous study in 2010—2011 with current 195 CAMP cases to investigate trends in the epidemiological features of CAMP in children in Taiwan.[15] (Table 3) The severity of CAMP in 2019—2020 was significantly lower in all respects, including laboratory data, image presentation, and hospital course (all $p < 0.001$). The 2010—2011 cohort defined MP infection as either a positive MP PCR and/or a positive serological response, which were more liberal than current study. Nevertheless, even with a relative smaller size, the 50 (39.4%) patients with positive PCR detection in 2010—2011 cohort showed a consistent higher severity compared to our enrolled patients. Three possible explanations could account for this difference. First, more timely administration of effective antibiotics was observed during 2019—2020 than 2010—2011. Although no macrolide resistance data are available for 2010—2011, we know that only 60.3% of patients were treated with macrolides. In contrast, during 2019—2020, 83% of the participants received effective antibiotics. Second, despite the increasing macrolide-resistant rate, the anti-inflammatory mechanism of macrolides may

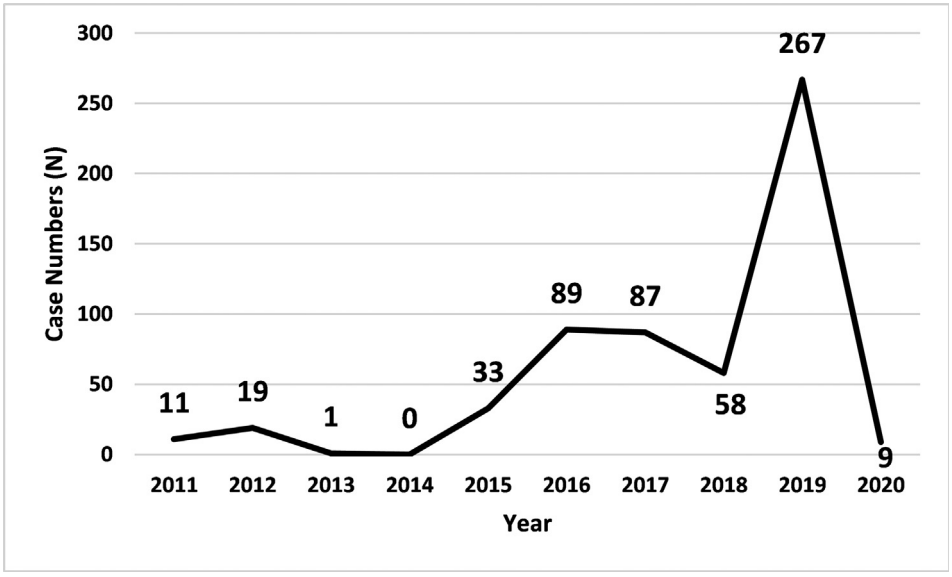

Figure 3. Annual distribution of patients with diagnosis of pneumonia due to *Mycoplasma pneumoniae* (ICD10:J157) infection in National Cheng Kung University Hospital, 2011–2020.

Table 2 Comparison of clinical outcomes of children with MRMP infection according to treatment timing.

	Delayed treatment[a] (n = 108; 77.1%)	Non-delayed treatment[a] (n = 32; 22.9%)	*p*
Duration of fever (days)	8.3 ± 3.0	7.5 ± 2.5	0.159
Hospital stay length (days)	5.3 ± 6.0	4.2 ± 1.7	0.302
ICU admission (n, [%])	3 (2.8)	0	>0.99
O_2 requirement (n, [%])	23 (21.3)	2 (6.3)	0.065
Severe disease[b]	24 (22.2)	2 (6.3)	**0.042***

[a] Delayed effective treatment refers to the lack of appropriate treatment within 5 days (<120 h) after fever onset.
[b] Severe MP infection was defined as severe respiratory symptoms warranting oxygen therapy, septic shock, or the need for intensive care.
**p* values in bold font indicate statistical significance.

Table 3 Comparison of clinical demographics and manifestations of CAMP between 2019–2020 and 2010–2011 epidemics.

	2019–2020 (N = 195)	2010–2011 (N = 127[a])	*p*
Age (years)	6.6 ± 3.8	6.1 ± 3.1	0.171
<2 years (n, [%])	12 (6.2)	2 (1.6)	0.054
>5 years (n, [%])	120 (61.5)	70 (55.1)	0.297
Sex (male) (n, [%])	98 (50.3)	58 (45.7)	0.427
Leukocytosis[b] (n, [%])	24 (12.3)	52 (40.9)	**<0.001***
Highest CRP (mg/dL)	47.3 ± 50.8	111.6 ± 112.9	**<0.001***
Duration of fever (days)	7.9 ± 3.5	8.3 ± 4.5	0.389
Hospital stay length (days)	4.9 ± 4.7	8.5 ± 7.5	**<0.001***
ICU admission (n, [%])	8 (4.1)	28 (22.0)	**<0.001***
O_2 requirement (n, [%])	32 (16.4)	51 (40.2)	**<0.001***
Consolidation[c] (n, [%])	100 (51.3)	86 (67.7)	**<0.001***
Pleural effusion (n, [%])	8 (4.1)	26 (20.5)	**<0.001***

[a] Of the 128 CAMP patients, one was not hospitalized and was later excluded.
[b] For age <5 years old, white blood cell count >15 000/μL; For age >5 years old, white blood cell count >11000/μL.
[c] Consolidation refers to patchy, lobular, or lobar opacity in chest x-ray.
**p* values in bold font indicate statistical significance.

contribute to better clinical outcomes when frequently prescribed in clinical setting.[27] Third, a recent study shows that clinical severity may differ between MP genotypes P1 type 1 and P1 type 2. However, determining whether strain shifting occurred in Taiwan between these study periods will require further investigation.[28]

The current study has limitations. First, current cohort only included patients with LRTIs that warranted hospitalization, which does not capture the complete spectrum of MP infections. Since mild cases can resolve spontaneously and patients treated effectively with macrolides may not require hospitalization, the macrolide resistance rate could be over-estimated in this study. Second, application of the high macrolide resistance observed in this study to the national scale would be premature, as it is based on local epidemiological data. Although we found no difference in clinical course between MRMP and MSMP infection with timely effective antimicrobial treatment, other factors, such as the disease severity upon initial presentation, might contribute to the clinical outcomes and disease course.

In conclusion, we observed an unusual surge in MP infection rates requiring pediatric LRTI hospitalizations during 2019—2020. Despite the higher rate of macrolide resistance, the clinical manifestations and severity of this MP epidemic outbreak were less severe than in 2010—2011. The increased prescription of macrolides or doxycycline as empiric antimicrobial therapy found during this recent epidemic is a possible explanation. Nevertheless, diagnosing acute MP infection by serological evidence alone may increase the rates of inappropriate and unnecessary antibiotic prescription, resulting in further increases in macrolide resistance.[14] Further studies exploring the appropriate antibiotic choice, optimal microbiological diagnostic method, assessments for macrolide resistance, and cost-effectiveness evaluation for MP infection will be needed to tailor national guidance and antimicrobial stewardship strategies.

Contributors' statement

C-YK, C-FS and C-CL contributed to the concept and design of the study; C-YK, W-CT and H-FL acquired the data and clinical materials. C-YK and H-FL carried out the statistical analysis. C-YK, C-FS and C-CL were responsible for drafting the manuscript. T-SH, L-MH, C-FS and C-CL revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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