Annual and seasonal patterns in etiologies of pediatric community-acquired pneumonia due to respiratory viruses and Mycoplasma pneumoniae requiring hospitalization in Korea

EUN LEE
Chonnam National University https://orcid.org/0000-0002-0145-7067
Chul-Hong Kim
Samsung Changwon Hospital
Yong Ju Lee
Hallym University College of Medicine
Hyo-Bin Kim
Inje University College of Medicine
Bong-Seong Kim
University of Ulsan College of Medicine
Hyung Young Kim
Pusan National University School of Medicine
Yunsun Kim
Soonchunhyang University Hospital
Sangyoung Kim
Soonchunhyang University Hospital
Chorong Park
Soonchunhyang University Hospital
Ju-Hee Seo
Dankook University Hospital
In Suk Sol
Hallym University Sacred Heart Hospital
Myongsoon Sung
Soonchunhyang University Hospital
Min Seob Song
Inje University College of Medicine
Dae Jin Song
Korea University College of Medicine and School of Medicine
Young Min Ahn Ahn
Eulji University College of Medicine
Hea Lin Oh
Korea Cancer Center Hospital
Jinho Yu
University of Ulsan College of Medicine

Sungsu Jung
Pusan National University School of Medicine
Kyung Suk Lee
Hanyang University College of Medicine
Ju Suk Lee
Samsung Changwon Hospital
Gwang Cheon Jang
National Health Insurance Corporation Ilsan Hospital
Yoon Young Jang
Catholic University of Daegu School of Medicine
Eun Hee Chung
Chungnam National University School of Medicine
Hai Lee Chung
Catholic University of Daegu School of Medicine
Sung-Min Choi
Dongguk University College of Medicine
Yun Jung Choi
Seoul National University College of Medicine
Man Yong Han
CHA Bundang Medical Center
Jung Yeon Shim
Kangbuk Samsung Medical Center
Jin-Tack Kim
Catholic University Uijeongbu St. Mary's Hospital
Chang-Keun Kim
Inje University College of Medicine
Hyeon-Jong Yang (pedyang@schmc.ac.kr)

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Abstract

Background: Community–acquired pneumonia (CAP) is one of the leading worldwide causes of childhood morbidity and mortality and its disease burden is affected by age and etiologies with time-dependent changes. We aimed to investigate the annual and seasonal patterns in etiologies of pediatric CAP requiring hospitalization. Methods: We conducted a retrospective study in 30,994 children (0-18 years old) with CAP between 2010 and 2015 at 23 nationwide hospitals in Korea. Mycoplasma pneumoniae (MP) pneumonia was clinically classified into macrolide-sensitive MP, macrolide-less effective MP (MLEP) and macrolide-refractory MP (MRMP) based on fever duration after initiation of macrolide treatment, regardless of the results of in vitro macrolide sensitivity tests.

Results: MP and respiratory syncytial virus (RSV) were the two most commonly identified pathogens of CAP. With the two epidemics of MP pneumonia (2011 and 2015), the rates of clinical MLEP and MRMP pneumonia showed increasing trends of 36.36% of the total MP pneumonia. In children less than 2 years of age, RSV (34.01%) was the most common cause of CAP, followed by MP (9.44%), whereas MP was the most common cause of CAP in children 2-18 years of age. Systemic corticosteroid was most commonly administered in MP pneumonia. The rate of hospitalization in intensive care unit was highest for RSV pneumonia, and ventilator care was most commonly needed in cases of adenovirus pneumonia.

Conclusions: The present study provides fundamental data for establishment of public health policies to decrease disease burden due to CAP as well as for improvement of pediatric health.

Background

Lower respiratory tract infections, including pneumonia, are a group of diseases that constitute a leading worldwide cause of pediatric morbidity requiring hospitalization and mortality [1, 2]. Childhood pneumonia causes diverse long-term sequelae, such as restrictive or obstructive lung disease, as well as bronchiectasis, particularly in a considerable proportion of children hospitalized due to community-acquired pneumonia (CAP) [3].

The etiologies of CAP affect the disease burden, development of long-term sequelae, and mortality [3, 4]. The mortality, severity, and disease burden due to CAP differ according to age, although CAP is caused by the same respiratory pathogens in all age groups [3, 5]. Therefore, prediction of the causative pathogens and clinical courses before confirmed identification of respiratory pathogens in children with CAP is needed to improve disease outcomes. There are annual and seasonal variabilities in the causative respiratory pathogens of CAP; moreover, the characteristics of causative respiratory pathogens, including sensitivity to antibiotics, change over time. Assessments of these annual and seasonal variabilities and pathogen characteristics could provide important information needed for establishment of direction of vaccine development and health care policy; however, comprehensive studies on these topics are lacking.

The most common causes of pediatric CAP are *Mycoplasma pneumoniae* (MP) and respiratory viruses [6]. Epidemics of MP infection are repeated on a 3–7 year cycle; the last epidemic in Korea was 2015 [7–9]. After 2000, macrolide-refractory MP (MRMP) pneumonia has become emergent with a rapidly increasing pattern, especially in Asia [7]. Currently, the rate of MRMP pneumonia in pediatric patients is estimated to be up to 80–90% [7–9]; thus, a new guideline is needed to aid in treatment strategies for MP pneumonia. MP infections in children are often self-limiting, even in patients with MRMP [10]. More than 80% of patients with macrolide-sensitive MP (MSMP) have shown defeverscence within 48–72 hours after the initiation of macrolide treatment; this occurs in approximately 30% of patients with MRMP [11]. Despite its high prevalence, large-scale epidemiologic studies of MRMP pneumonia are lacking.

In the present study, we aimed to identify the annual and seasonal patterns of respiratory pathogens in pediatric CAP requiring hospitalization, and the prevalence of MRMP. In addition, we compared the clinical characteristics associated with specific respiratory pathogens in patients with pediatric CAP.

Methods

Study population

We conducted a retrospective chart review of children hospitalized with CAP between 1 January 2010 and 31 December 2015 in a cohort of children younger than 18 years of age from 23 medical centers in Korea. During the study period, a total of 65,243 children were diagnosed with CAP based on clinical features, chest radiography, and laboratory findings. Among them, 30,994 children underwent real-time polymerase chain reaction (RT-PCR) analyses for respiratory virus or MP, or underwent serology tests for MP, in order to identify the etiologies of CAP [7]. The enrolled children were further divided into four age groups as follows, in order to identify differences in causative pathogens according to age: less than 2 years of age, between 2 and 5 years, between 5 and 12 years, and between 12 and l8 years of age. Information regarding the clinical characteristics, radiologic findings, and laboratory findings was collected from the electronic medical record. The Institutional Review Boards of all participating medical centers reviewed and approved the study protocol.

Definition

Pneumonia was diagnosed by pediatricians based on both physical examinations and radiologic assessments. MP infection was defined as pneumonia in which at least one of the following criteria was met: (1) positive results in both RT-PCR analysis of nasopharyngeal samples and specific IgM against MP at the time of hospitalization due to CAP, (2) seroconversion of specific IgM against MP, or (3) four-fold or greater increase in specific IgG against MP in the acute and convalescent stages.

The clinical courses of MP pneumonia have shown heterogeneous features, even in patients with the same results of in vitro sensitivity to macrolide [8, 9, 12]. Some previous studies have shown no significant differences in clinical, laboratory, and radiologic features between children with MRMP pneumonia and those with MSMP pneumonia [7–9]. Therefore, to characterize the clinically heterogeneous MP pneumonia into more homogenous groups in real clinical world, we defined clinical MSMP, MRMP, and macrolide less-effective MP (MLEP) pneumonia according to fever duration in each pneumonia episode, regardless of the sensitivity test for macrolide, as follows: fever for less than 3 days, fever for more than 7 days, and more than 3 days but less than 7 days, respectively.

Microbiological studies

The results of RT-PCR during hospitalization were reviewed. The identified respiratory viruses were as follows: adenovirus (AdV), human rhinovirus (HRV), influenza virus (FLU), parainfluenza virus (PIV), human metapneumovirus (HMPV), respiratory syncytial virus (RSV), bocavirus (BoV), and human coronavirus (HCoV). The results of RT-PCR analyses and serologic titers for MP infection were obtained from comprehensive reviews of laboratory records.

Statistical analysis

Seasonal Mann-Kendall tests, a type of non-parametric statistical analysis, were used to detect monotonic trends in monthly time series data with an annual seasonal pattern. For the categorical variables, numbers and percentages were summarized and groups were analyzed using the chi-squared test. Post hoc analyses were used to examine if the characteristics of MP pneumonia groups were statistically significant with chi-squared test. For the continuous variables, mean and standard deviation (SD) were derived, and one-way ANOVA tests were conducted to compare groups, followed by Bonferroni's post hoc test. In such cases, the non-parametric Kruskal-Wallis rank test was performed, followed by with Dunn's post hoc test. All statistical analyses were performed using R 3.5.1. A *p* value of <0.05 was considered statistically significant.

Results

Characteristics of the study population

During the study period, a total of 30,994 children with CAP requiring hospitalization were enrolled in the present study. The characteristics of the study population are presented in Table 1. The mean age of the study population was 41.9 months (SD, 40.8 months). A total of 54.6% of the study population were boys. The number of children hospitalized due to CAP was highest in fall (September to November), followed by winter (December to February), spring (March to May), and summer (June to August).

Annual and seasonal patterns of CAP caused by respiratory virus and MP

During the study period, the number of children hospitalized due to CAP was highest in 2011, followed by 2015 (Figure 1). The number of children hospitalized with CAP due to various respiratory virus infections was highest in 2015, with similar seasonal and annual patterns of total CAP. Among the various respiratory viruses, RSV was the most commonly identified virus, especially from November to December, with a gradually increasing trend until each peak (Figure 2). The number of children hospitalized due to FLU-associated CAP peaked from January to March in each year, with the largest number of affected patients in 2015; the number of children hospitalized with HMPV-associated CAP peaked in April, with its largest number of affected patients in 2014 (Supplementary Figure 1).

The two epidemics of MP pneumonia (2011 and 2015) corresponded with the two peaks of CAP. The incidence of MP pneumonia requiring hospitalization in children peaked from October to November in each year (Figure 1). The most common clinical phenotype of MP pneumonia was MSMP, followed by MLEP and MRMP (Figure 3A). During the study period, the rate of MSMP/total MP pneumonia was 63.6–100.0% (mean ± SD, 81.3 ± 7.7), that of MRMP/total MP pneumonia was 0.0–11.0% (4.2 ± 4.3), and that of MLEP/total MP pneumonia was 0.0–30.3% (14.5 ± 14.2) (Figure 3B). The rates of clinical MLEP and MRMP pneumonia showed increasing trends (seasonal Mann-Kendall trend tests, $P = 0.0644$ and $P = 0.0066$, respectively), whereas that of clinical MSMP pneumonia showed a significant reduction during the study period (seasonal Mann-Kendall trend test, $P = 0.0028$).

Causative pathogens of CAP according to age

The number of children hospitalized with CAP decreased with age (Table 2). In children aged less than 2 years of age, RSV (34.0%) was the most commonly detected respiratory pathogen, followed by PIV (19.7%) and HRV (18.8%). In

children 2–4 years of age, RSV (14.9%) was the most commonly identified respiratory virus, followed by HRV (14.8%) and PIV (13.6%). In children 5–17 years of age, HRV was the most commonly detected virus, followed by FLU.

In children more than 2 years of age, MP was the most common etiology of CAP, whereas 9.44% of children less than 2 years of age exhibited MP infection. The rate of clinical MRMP/total MP pneumonia was highest in children 5–9 years of age (244/3475, 9.8%), followed by adolescents 10–17 years of age (47/905, 6.9%), children 2–4 years of age (154/3526, 4.4%) and those less than 2 years of age (25/1277, 2.0%).

Clinical characteristics and laboratory findings according to etiologies of CAP

The clinical features and laboratory findings, according to etiologies, in children admitted due to CAP are described in Table 3. The median length of hospital stay due to CAP was 181.39 hours. The duration of hospitalization due to CAP was longest in AdV pneumonia, followed by RSV pneumonia. Systemic corticosteroid was most commonly administered in MP pneumonia (n = 1645, 22.1%), followed by RSV pneumonia (n = 622, 13.8%). The number of children with CAP who required oxygen supplementation was largest in RSV pneumonia (n = 905, 20.0%); ventilator care was most commonly applied in AdV pneumonia (n = 13, 1.9%), followed by RSV pneumonia (n = 119, 2.6%).

The levels of whole blood counts were highest in AdV, followed by RSV, FLU, HMPV, and MP. Neutrophil levels (%) were highest in MP, followed by FLU, AdV, HMPV, and RSV. C-reactive protein levels were highest in MP, followed by AdV, HMPV, FLU, and RSV.

Discussion

We evaluated the annual and seasonal patterns in respiratory etiologies of pediatric CAP requiring hospitalization between 2010 to 2015 in a nationwide retrospective cohort study. When bacterial pneumonia was excluded, the most common causes of hospitalization due to pediatric CAP were RSV and MP, with peaks in October-November and November-December, respectively. There were two epidemics of MP pneumonia (2011 and 2015) during the study period. In children hospitalized with CAP due to MP pneumonia, the rates of clinical MRMP and MLEP pneumonia showed increasing trends, together comprising approximately 36% of the total MP pneumonia. In children less than 2 years of age, RSV was the most common cause of pediatric CAP requiring hospitalization, whereas the most common cause was MP in children older than 2 years, as well as in adolescents. The rate of children admitted to the intensive care unit was highest in children with RSV pneumonia, followed by those with AdV pneumonia. Ventilator care was most commonly needed in children with AdV pneumonia, followed by those with RSV pneumonia. The results of the present study provide fundamental data on the periodicity of epidemics of causative pathogens of pediatric CAP requiring hospitalization, which may be helpful for the prediction of future epidemic of causative respiratory pathogens of pediatric CAP and establishment of policies to reduce the disease burden due to pediatric CAP, which is one of the major causes of morbidity and mortality in children.

In the present study, we found that RSV was the most common cause of disease burden in children younger than 2 years of age, which is consistent with the findings of other studies performed in other countries, regardless of the detection methods used or national income levels of the children who were analyzed [6, 13]. The disease burden due to RSV pneumonia was higher than that caused by other respiratory pathogens in that the rates of ventilator care and oxygen supplementation were highest, and the rate of admission to the intensive care unit was the second highest among children in the present study. The immune responses in RSV infection differ according to age [14]. Notably,

inefficient and ineffective immune responses in early life contribute to more severe disease and more frequent occurrences of RSV infection; this is especially problematic in infants, who are most frequently affected by RSV pneumonia [14]. These findings may be valuable to guide therapeutic approaches and prevention strategies in children with CAP; moreover, they suggest that the development of strategies to prevent RSV infection, especially in infants or younger children, might aid in decreasing the worldwide disease burden due to CAP.

The number of children hospitalized with MP pneumonia was typically highest between October and November. In the previous studies, the peak incidence of MP pneumonia showed a similar pattern to that observed in the present study, regardless of age [13, 15]. However, in the 2011 Korean epidemic, the peak rate of hospitalization due to MP pneumonia in children occurred in September, whereas the peak rate in the 2015 epidemic occurred in November. In addition, the number of children hospitalized with MP pneumonia in the 2015 epidemic was smaller than that in the 2011 epidemic. These findings were similar to those revealed in another study [15], and suggest that there were differences in the seasonality of MP pneumonia between each of the two epidemics, and that the peak number of patients with MP pneumonia differed between the two epidemics. The reasons for these phenomenon may be the increased presence of protective immunity after the first epidemic, which might have played a role in the second epidemic, although the increased protective immunity may not have lasted long [7].

Based on in vitro macrolide sensitivity tests, the macrolide resistance rates of MP pneumonia have recently been identified as 50–90% [7, 8]; these largely differ among nations. When we defined clinical MSMP, MLEP, and MRMP according to fever duration in each pneumonia episode, regardless of the antibiotics administered and results of in vitro macrolide sensitivity tests, the ratios of clinical MLEP and MRMP to total MP pneumonia showed increasing trends after adjustment for monthly time series. However, the ratio of clinical MRMP pneumonia, estimated as 0.0–11.0% in the present study, was far lower than that based on in vitro macrolide sensitivity tests [7, 8]. Therefore, the results of our present study suggest that the real world clinical response of MP pneumonia to macrolide treatment might not be as weak as that has been reported, based on in vitro macrolide sensitivity tests. Due to its high prevalence of MRMP, there is a great deal of concerns regarding second-line treatment options for MRMP, including tetracycline or fluoroquinolones; however, the use of these drugs in children has been prohibited by the United States Food and Drug Administration [7]. Some previous studies have reported no significant differences with respect to clinical and radiologic findings between MRMP and MSMP pneumonia in children [8, 9]. When combined with the results of the present and previous studies [8, 12], a considerable proportion of cases of MRMP pneumonia might be recategorized as clinical MSMP or MLEP pneumonia. Therefore, first-line treatment for MP pneumonia can be initially started, even in cases of MRMP pneumonia. Considering the exaggerated immune responses in children with MP pneumonia [16], application of immune-modulators, such as corticosteroids or immunoglobulin, rather than antibiotics, might play a more important role in the management of MP pneumonia, even in some cases of MLEP or MRMP pneumonia [17]. When selecting the proper treatment strategies for MP pneumonia, consideration of diverse clinical courses including self-limiting and combined exacerbated immune responses in each case, might be more important than the simple results of in vitro sensitivity tests to macrolide.

This study has some limitations. First, there might have been selection bias due to miss of some cases, although this study included 23 nationwide secondary and tertiary hospitals. Second, some patients might have been misclassified into the “no MP pneumonia and no respiratory virus detection” group due to sampling error, including inappropriate sputum specimens or lack of repetitive follow-up of MP-specific IgM in patients with initial negative results for MP-specific IgM. In the present study, we did not include CAP caused by bacterial pathogens; therefore, we could not identify time-dependent changes in the occurrence of CAP caused by bacterial pathogens alone or caused by co-infection of bacteria and viruses. However, following the introduction of the Pneumococcal conjugate vaccine and *Haemophilus influenza* type b vaccine, the disease burden due to bacterial pneumonia has significantly decreased [6,

18]. In the present study, in vitro resistance testing of MP was not performed in some cases. Therefore, we clinically defined MSMP, MRMP, and MLEP pneumonia groups solely on the basis of fever duration after initiation of the administration of macrolide, regardless of the results of in vitro tests for macrolide sensitivity. Because the results of in vitro sensitivity tests to antibiotics do not always correspond with those of in vivo sensitivity tests of the same antibiotics [19], and administration of immune-modulators might play a more important role in the treatment of MP pneumonia in some cases, application of clinical classifications of MP pneumonia, rather than the results of in vitro macrolide sensitivity tests, might be more helpful in the management of MP pneumonia, especially in cases of MLEP and MRMP pneumonia, in this era with a high rate of antibiotic- refractory MP.

Conclusions

We identified the annual and seasonal patterns of pediatric CAP requiring hospitalization. Throughout the study period, MP and RSV were the most common causes of CAP, with cyclic peaks in specific seasons. The disease burden due to pediatric CAP requiring hospitalization is largely due to RSV pneumonia, especially in infants and young children. The relatively lower rate of clinical MLEP and MRMP pneumonia, contrary to the known high prevalence of MRMP, arouses attention to the treatment strategies for patients with MP pneumonia. The results of the present study may aid in establishing treatment and management strategies for pediatric CAP in children and policies to reduce the disease burden by improving public health approaches for children.

Abbreviations

AdV: Adenovirus

BoV: Bocavirus

CAP: community acquired pneumonia

Flu: influenza virus

HCoV: Human coronavirus

HMPV: human metapneumovirus

HRV: human rhinovirus

MLEP: macrolide less effective *Mycoplasma pneumoniae*

MP: *Mycoplasma pneumoniae*

MRMP: macrolide-refractory *Mycoplasma pneumoniae*

MSMP: macrolide-sensitive *Mycoplasma pneumoniae*

PIV: parainfluenza virus

RSV: respiratory syncytial virus

RT-PCR: real-time polymerase chain reaction

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board and Ethics Committee of Soonchunhyang University Seoul Hospital (SCHUH201–309013001). The informed consent was waived because this study was a retrospective medical chart review study with no personal information in each participant.

Consent for publication

Not applicable

Availability of data and materials

The data used were collected through the routine surveillance systemic of Pneumonia & Respiratory Disease Study Group of Korean Academy of Pediatric Allergy and Respiratory Disease. Dara are available from the authors upon reasonable request and with permission of the Pneumonia & Respiratory Disease Study Group of Korean Academy of Pediatric Allergy and Respiratory Disease.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived and designed the experiments: EL, CHK, YJL, HBK, BSK, HYK, YSK, SYK, CRP, JHS, ISS, MSS, MSS, DJS, YMA, HLO, JHY, SSJ, KSL, JSL, GCJ, YYJ, EHC, HLC, SMC, YJC, MYH, JYS, JTK, CKK, and HJY. Performed the experiments: EL, CHK, YJL, HBK, BSK, HYK, YSK, SYK, CRP, JHS, ISS, MSS, MSS, DJS, YMA, HLO, JHY, SSJ, KSL, JSL, GCJ, YYJ, EHC, HLC, SMC, YJC, MYH, JYS, JTK, CKK, and HJY. Contributed reagents/materials/analysis tools: YSK, SYK, and CRP. Contributed to the writing of the manuscript: EL, CHK, CRP and HJY. All authors contributed to manuscript revisions.

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Tables

Table 1. Demographic characteristics of hospitalized children with community-acquired viral and *Mycoplasma pneumoniae* pneumonia

Variables	No. (%) or mean ± SD
Number	30,994
Age (mo), mean ± SD	41.87 ± 40.84
< 2 yrs	13,527 (43.64)
2 yrs ≤ age <5 yrs	9,715 (31.34)
5 yrs ≤ age <12 yrs	5,802 (18.72)
12 yrs ≤ age <18 yrs	1,950 (6.29)
Sex (male), No. (%)	16,929 (54.62)
Incident year, No. (%)	30,991 (100.00)
2010	4,001 (12.91)
2011	6,427 (20.74)
2012	3753 (12.11)
2013	2913 (9.40)
2014	5702 (18.40)
2015	8195 (26.44)
Incident season	30994 (100.0)
Spring (Mar, Apr, May)	7765 (25.05)
Summer (Jun, Jul, Aug)	5124 (16.53)
Fall (Sep, Oct, Nov)	10065 (32.47)
Winter (Dec, Jan, Feb)	8040 (25.94)

Mo, months; n, number; SD, standard deviation, yrs, years.

Table 2. Prevalence of causative respiratory pathogens according to age groups in children hospitalized due to community-acquired pneumonia

Detected respiratory virus	<2 years, No. (%)	2-4 years, No. (%)	5-9 years, No. (%)	10-17 years, No. (%)	Total, No. (%)
Adenovirus	964 (7.1)	764 (7.9)	183 (3.12)	33 (1.7)	1,944 (6.3)
Rhinovirus	2,545 (18.8)	1,441 (14.8)	626 (10.8)	199 (10.2)	4,811 (15.5)
Influenza	701 (5.2)	619 (6.44)	519 (9.0)	196 (10.1)	2,035 (6.6)
Influenza A	534 (4.0)	386 (4.0)	302 (5.2)	117 (6.00)	1,339 (4.32)
Influenza B	172 (1.3)	239 (2.5)	218 (3.8)	79 (4.1)	708 (2.3
Parainfluenza	2,668 (19.7)	1,317 (13.6)	476 (8.2)	192 (9.9)	4,653 (15.0)
Metapneumovirus	1,049 (7.8)	750 (7.7)	112 (1.9)	45 (2.3)	1,956 (6.3)
Respiratory syncytial virus	4,600 (34.0)	1,451 (14.9)	194 (3.3)	59 (3.0)	6,304 (20.3)
Bocavirus	511 (38)	214 (2.2)	41 (0.7)	20 (1.0)	786 (2.5)
Coronavirus	264 (2.0)	152 (1.6)	66 (1.1	21 (1.1)	503 (1.6)
MP	1,277 (9.44)	3,526 (36.3)	3,475 (59.9)	905 (46.4	9,183 (29.6)
Clinically MSMP	1,121 (8.3)	2,816 (28.99)	2,482 (42.8)	681 (34.9)	7,100 (22.9
Clinically MRMP	25 (0.2)	154 (1.6)	244 (4.2)	47 (2.4)	470 (1.5)
Clinically MLEP	131 (1.10)	556 (5.7)	749 (12.9)	177 (9.1)	1,613 (5.2)
Not identified both MP and virus	1,997 (14.8)	1,529 (15.7)	906 (15.6)	484 (24.8)	4,916 (15.9)
Only respiratory virus detection	10,253 (75.8)	4,660 (48.0)	1,421 (24.5)	561 (28.8)	16,895 (54.5)
Total number	13,527 (100.0)	9,715 (100.0)	5,802 (100.0)	1,950 (100.0)	30,994 (100.0)

MLEP, macrolide less effective *Mycoplasma pneumoniae*; MP, *Mycoplasma pneumoniae*; MRMP, macrolide refractory *Mycoplasma pneumoniae*; MSMP, macrolide sensitive *Mycoplasma pneumoniae*

Table 3. Comparison of clinical and laboratory findings according to respiratory pathogens in children hospitalized due to community-acquired pneumonia

Variables	only MP[1]	MP coinfected with virus[2]	Adenovirus[3]	Influenza virus[4]	Metapneumovirus[5]	RSV[6]	*P* value	Post hoc test[a]
Age (month), mean ± SD	66.7 ± 39.7	53.3 ± 37.3	34.1 ± 28.0	54.4 ± 46.0	28.1 ± 28.2	15.9 ± 21.0	<0.0001	1>4=2>3>5>6
Sex (male), No. (%)	3,680 (49.4)	862 (49.9)	389 (57.2)	828 (55.5)	692 (53.8)	2,551 (56.4)	<0.0001	2>3=6=4=5>1
Duration of Hospitalization (hrs), mean ± SD	159.9 ± 227.40	174.2 ± 339.8	181.4 ± 250.4	136.3 ± 161.2	148.6 ± 166.0	162.2 ± 238.6	<0.0001	3=2=6=1≥5≥4
Administration of steroid, No. (%)	1,645 (22.1)	454 (26.3)	75 (11.0)	117 (7.9)	170 (13.2)	622 (13.8)	<0.0001	2>1>6=5=3>4
Oxygen supplementation, No. (%)	299 (4.0)	109 (6.3)	67 (9.9)	82 (5.5)	147 (11.4)	905 (20.0)	<0.0001	6>5>3>2=4=1
Ventilator care, No. (%)	12 (0.2)	4 (0.2)	8 (1.2)	14 (0.9)	12 (0.9)	51 (1.1)	<0.0001	3=6>4=5=2=1
ICU care, No. (%)	27 (0.4)	11 (0.6)	13 (1.9)	23 (1.5)	17 (1.3)	119 (2.63)	<0.0001	6≥3=4=5=2>1
WBC ($x10^3/\mu L$) mean ± SD	9,426.3 ± 4,669.2	10,120.5 ± 5,068.8	12,802.1 ± 5,773.9	8,293.5 ± 4,004.4	9,542.4 ± 4,510.8	10,417.0 ± 4,248.5	<0.0001	3>6=2>5=1>4
Neutrophil (%), mean ± SD	58.2 ± 16.8	55.5 ± 18.2	55.0 ± 18.3	55.4 ± 20.7	43.4 ± 19.4	37.1 ± 19.0	<0.0001	1>2=4=3>5>6
Lymphocyte (%), mean ± SD	30.6 ± 14.3	33.3 ± 16.1	34.8 ± 16.9	32.3 ± 18.6	45.2 ± 17.6	51.5 ± 97.5	<0.0001	6>5>3≥2≥4>1
Eosinophil (%), mean ± SD	2.7 ± 3.0	2.2 ± 3.1	1.3 ± 2.4	1.1 ± 1.9	1.1 ± 1.7	1.7 ± 2.1	<0.0001	1>2>6=3=5=4
Hb, mean ± SD	12.4 ±1.0	12.3 ± 1.1	11.7 ± 1.1	12.2 ± 1.2	11.9 ± 1.2	11.9 ± 1.4	<0.0001	1≥2≥4>5≥6≥3
Platelet ($x10^3/\mu L$), mean ± SD	298.5 ± 125.4	294.1 ± 111.8	301.0 ± 139.2	244.7 ± 95.8	270.8 ± 124.2	327.6 ± 149.5	<0.0001	6>3=1=2>5>4
AST, U/L, mean ± SD	42.8 ± 121.4	44.2 ± 103.5	44.8 ± 68.8	48.7 ± 230.3	49.8 ± 126.2	46.2 ±45.5	0.2552	NA
ALT , U/L, mean ± SD	27.0 ± 116.2	28.0 ± 105.9	29.7 ± 92.8	26.9 ± 109.4	27.8 ± 85.1	29.8 ± 50.1	0.7792	NA
LDH, U/L, mean ± SD	531.5 ± 379.8	540.9 ± 339.6	548.8 ± 315.5	462.8 ± 292.0	561.5 ± 302.3	534.9 ± 205.1	<0.0001	5=3=2=6=1>4
CRP, mg/dL, mean ± SD	8.2 ± 19.9	5.4 ± 13.0	7.3 ± 27.1	3.5 ± 8.1	3.9 ± 9.0	2.5 ± 7.5	<0.0001	1≥3≥2≥5≥4
ESR, mm/hr,, mean ± SD	34.4 ± 22.5	34.0 ± 22.7	38.1 ± 26.2	18.5 ± 17.5	24.5 ± 20.1	20.7 ± 19.3	<0.0001	3>1=2>5>6

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; ICU, intensive care unit; LDH, lactate dehydrogenase; MP, *Mycoplasma pneumoniae*; NA, not applicable; RSV, respiratory syncytial virus; SD, standard deviation; WBC, whole blood count.

[a]Group 1, MP pneumonia; group 2, MP co-infected with virus; group 3, adenovirus; group 4, influenza virus; group 5, Metapneumovirus; group 6, RSV.

[b]Post hoc analyses were used to examine if the characteristics of MP pneumonia groups were statistically significant with chi-squared test. For the continuous variables, mean and standard deviation (SD) were derived, and one-way ANOVA tests were

conducted to compare groups, followed by Bonferroni’s post hoc test.

Figures

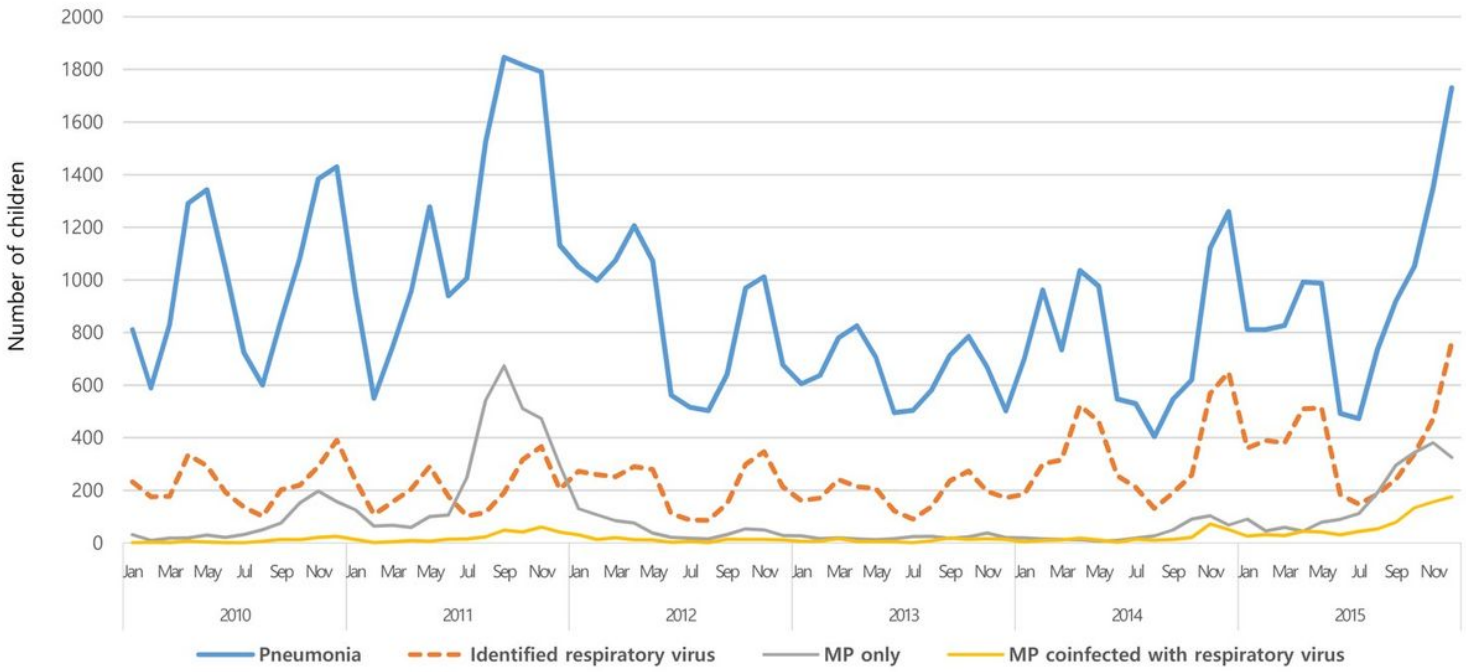

Figure 1

Number of children hospitalized with community-acquired pneumonia according to etiology between 2011 and 2015 in Korea

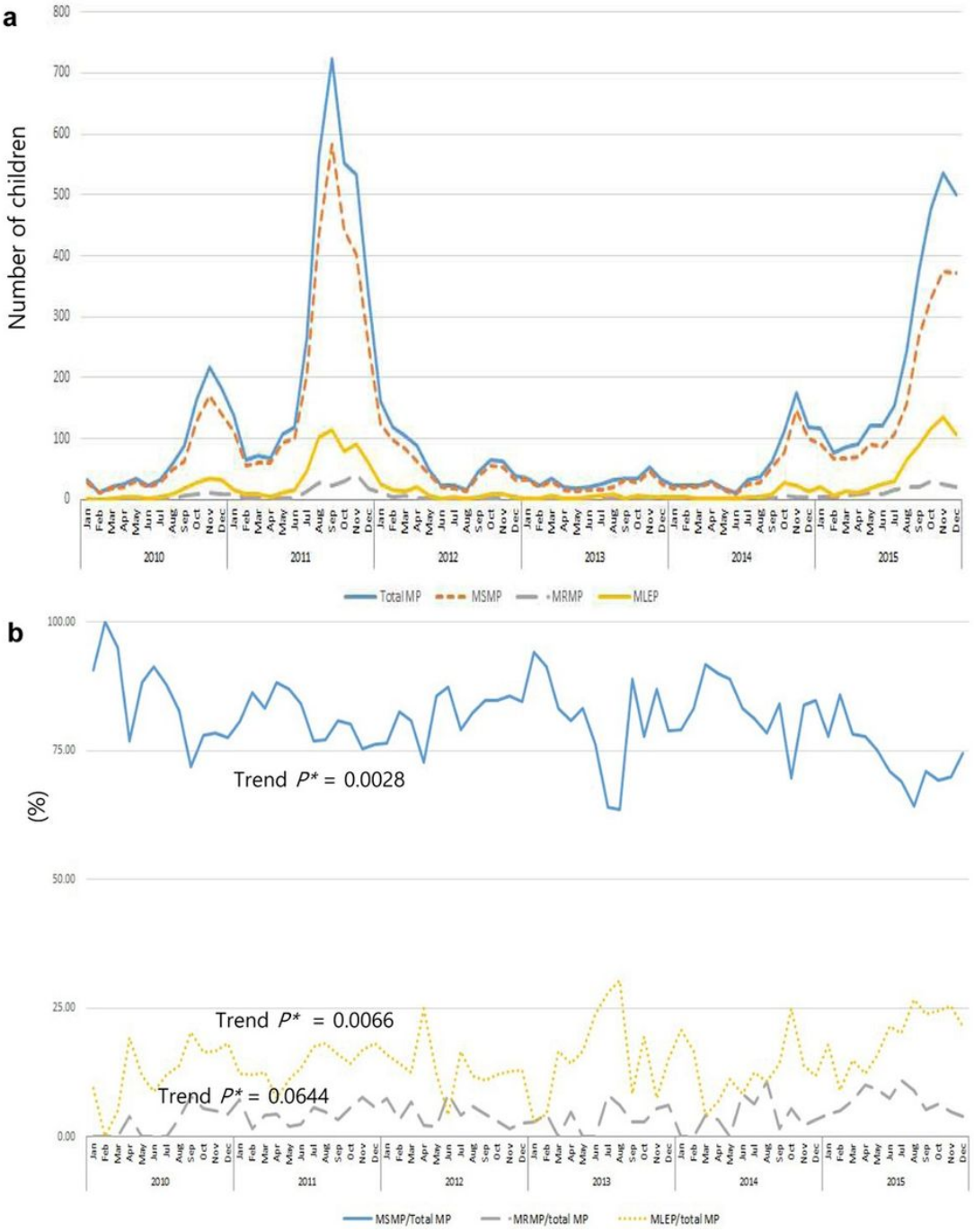

Figure 2

Number of children hospitalized with community acquired pneumonia according to etiology

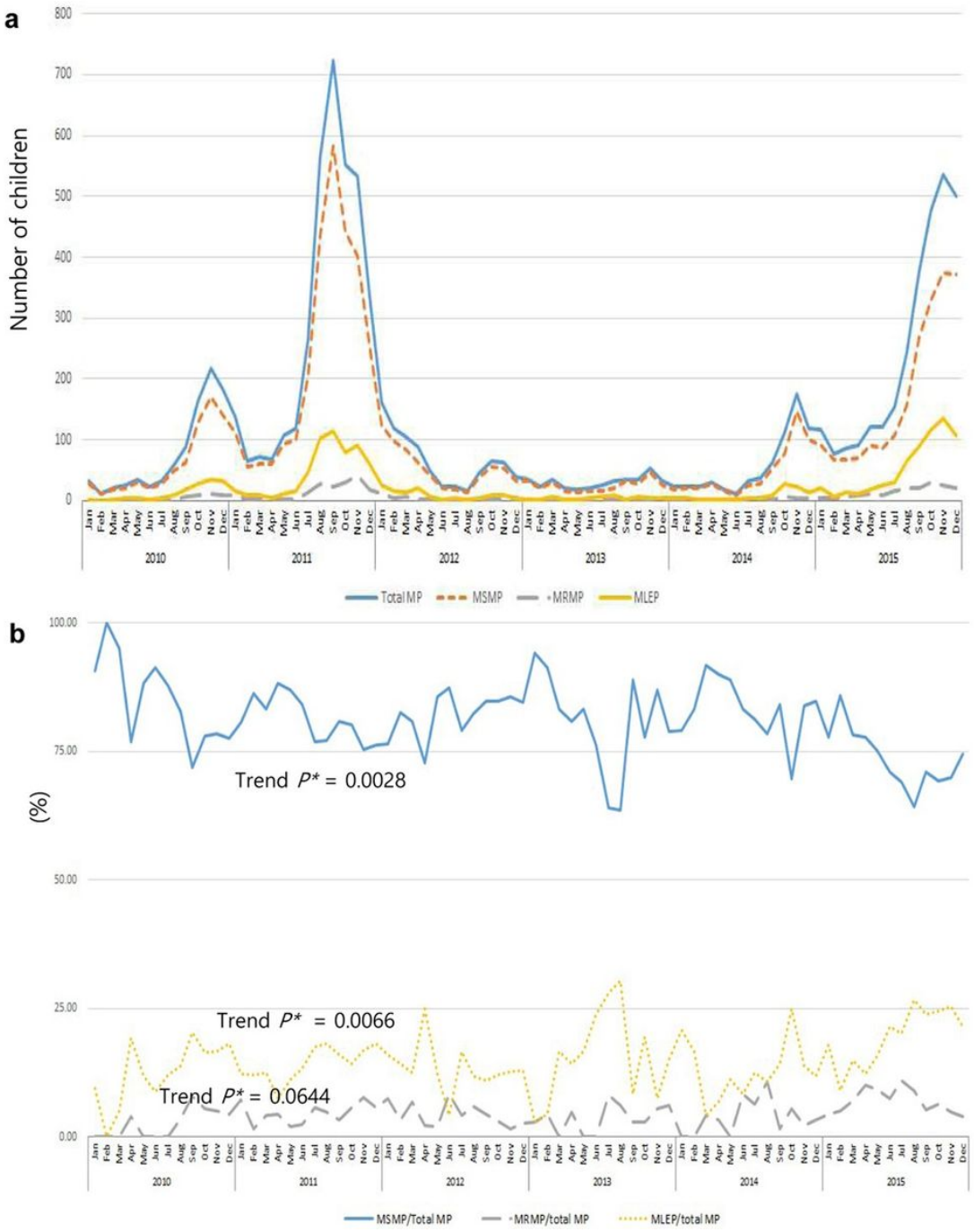

Figure 3

Time-dependent changes in the numbers of children hospitalized due to Mycoplasma pneumoniae (MP) pneumonia pneumonia according to clinical macrolide sensitivity. (A) Number of children hospitalized with MP pneumonia classified as macrolide-sensitive (MSMP), macrolide- refractory (MRMP), and macrolide less-effective (MLEP). (B) Time-dependent changes in the ratios of MSMP/total MP pneumonia, MRMP pneumonia/total MP pneumonia, and MLEP pneumonia/total MP pneumonia during the study period.

Supplementary Files

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