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Original Article

Assessing the utilization of antimicrobial agents in pediatric pneumonia during the era of the 13-valent pneumococcal conjugate vaccine: A retrospective, single-center study

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Abstract *Background and purpose:* Pneumonia and bronchopneumonia are the most common infectious diseases in children. This study aimed to analyze changes in causative pathogens and antibiotic use for bronchopneumonia or pneumonia after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in children.
Methods: This retrospective study was conducted from 2009 to 2019. Hospitalized children aged 6 months–3 years with a discharge diagnosis of bronchopneumonia or pneumonia were included to analyze changes in the potential mismatch between the diagnosed pathogen and antibiotic use.
Results: The cohort comprised 1100 patients, including 648 (59%) and 452 (41%) with a discharge diagnosis of bronchopneumonia and pneumonia, respectively. The trend of viral pneumonia increased every year ($r_s = 0.101$, $p < 0.05$) Antibiotics were administered in 97% patients, with an increasing annual trend in macrolide use ($r_s = 0.031$, $p = 0.009$). Regarding antibiotic utilization, no significant variations were observed in the days of therapy (DOT) ($r_s = 0.076$, $p = 0.208$) or length of therapy (LOT) ($r_s = -0.027$, $p = 0.534$) per patient-year throughout the study duration. Interestingly, the LOT for combined therapy with macrolides and first-line beta-lactams was high ($r_s = 0.333$, $p = 0.028$). In viral pneumonia treatment, neither the DOT nor LOT exhibited significant variations ($r_s = -0.006$, $p = 0.787$ and $r_s = -0.156$, $p = 0.398$).

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Conclusion: After the introduction of PCV13 in Taiwan, no decrease in antibiotic use has been observed among children aged 6 months—3 years with a discharge diagnosis of bronchopneumonia and pneumonia.

Introduction

Pneumonia and bronchopneumonia are the most prevalent infectious diseases affecting pediatric populations. According to the World Health Organization, in 2019 these diseases caused 740,180 deaths in children below five years of age, accounting for 14% of all deaths in this age range.[1,2] *Streptococcus pneumoniae* is regarded as the most important pathogen associated with these infections and can lead to severe conditions, including death.[3,4] Importantly, vaccines against *S. pneumoniae* have contributed to reduced morbidity and mortality.[4,5]

As recommended by the Advisory Committee on Immunization Practices in Taiwan, in 2013 a government-funded program including 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in pediatric patients aged 2—5 years. In 2014, the age category was expanded to one year of age. The three-dose PCV13 immunization schedule was established as a routine vaccination protocol in 2015, with the first two doses administered at 2 and 4 months of age, respectively, and the third dose administered between 12 and 15 months of age.[4—7] According to the National Vaccination Coverage Report in Taiwan, the proportion of children immunized with PCV13 has remained high, with consistent initial dose coverages of 96.4%, 98%, 97.9%, and 98.2% and annually increasing booster dose coverages of 93.3%, 95.8%, 95.8%, and 96.4% in 2016, 2017, 2018, and 2019, respectively.[8]

The introduction of PCV13 in Taiwan has led to a considerable decrease in the incidence of invasive pneumococcal disease (IPD). According to the data obtained from the Taiwan Centers for Disease Control (Taiwan CDC), the incidence of IPD in young children aged 2—5 years has notably decreased by up to 50%, decreasing from 22.8 per 100,000 persons in 2011—2012 to 11.9 per 100,000 persons in 2013. Furthermore, the incidence of IPD among children aged >5 years has decreased by 70%, with a decrease from 20.8 per 100,000 persons in 2011 to 6.2 per 100,000 persons in 2015.[9] A recent pediatric epidemiologic study in Northern Taiwan also revealed a significant decrease in the number of hospitalizations due to *S. pneumoniae* after the introduction of the free PCV13 immunization policy for children.[10]

Besides *S. pneumoniae*, several other pathogens have been identified that cause pneumonia in children that leads to hospitalization. Over the past decade, the prevalence of pnuemonia caused by various pathogens such as *Mycoplasma pneumoniae*, adenovirus, and several types of respiratory viruses (influenza, respiratory syncytial virus, and parainfluenza) has been increasing in children with pneumonia.[10] After careful consideration, it is reasonable to expect that the use of antibiotics and prevalence of bacterial pneumonia among children should decrease with the introduction of the PCV13 vaccine.[10] A systematic literature review in 2020 studied various patterns of antimicrobial usage following vaccination and revealed that 12 of the 13 reviewed studies reported a decline in the use of antimicrobials, as indicated by at least one of the used assessment measures.[11] However, studies regarding such cases in real-world setting in Taiwan are scarce.[12]

The inappropriate use of antibiotics has exacerbated the issue of antibiotic resistance, making it a concerning and growing threat to public health.[13] Antimicrobial stewardship programs (ASPs) play a crucial role in counteracting this issue.[12] These programs quantify antibiotic consumption using metrics such as days of therapy (DOT) per patient-year and length of therapy (LOT) per patient-year. These metrics provide a reliable assessment of the utilization of multiple antibiotics and the duration of therapy.[13,14]

This study aimed to examine the demographic characteristics, length of hospitalization, disease severity, causative pathogens, and antibiotic usage in hospitalized pediatric patients with pneumonia or bronchopneumonia before and after the phased implementation of PCV13 over a period of 11 years.

Methods

Study design

This retrospective study was conducted at MacKay Children's Hospital in Taiwan between January 01, 2009 and December 31, 2019. The ethics approval was obtained from MacKay Memorial Hospital Institutional Review Board, and informed consent was waived because of the retrospective nature of the study (approval no: 22MMHIS058e). The study cohort included children aged 6 months to 3 years who were hospitalized and met the discharge diagnosis of pneumonia or bronchopneumonia during the study period of 11 years. Children with renal, cardiac, hematologic, neoplastic, or immunologic disorders and those with prematurity-related chronic lung disease were excluded. The flow chart of the study's inclusion and exclusion processes is shown in Fig. 1.

Demographic and clinical data, such as age, sex, diagnosis, length of hospitalization, identified pathogens, and antibiotic use, were collected from medical records. Data on laboratory tests at presentation, including white blood cell (WBC) and absolute neutrophil counts, and C-reactive protein (CRP) level, were also collected.

The length of the hospital stay was measured in days. The mean hospital stay duration is determined by dividing the sum of number of days all patients were hospitalized by the total number of patients.

The sample size was calculated based on a type-I error of 0.05 and power of 80%, while assuming the reduction in DOT for antibiotic use. Due to yearly variations in the total

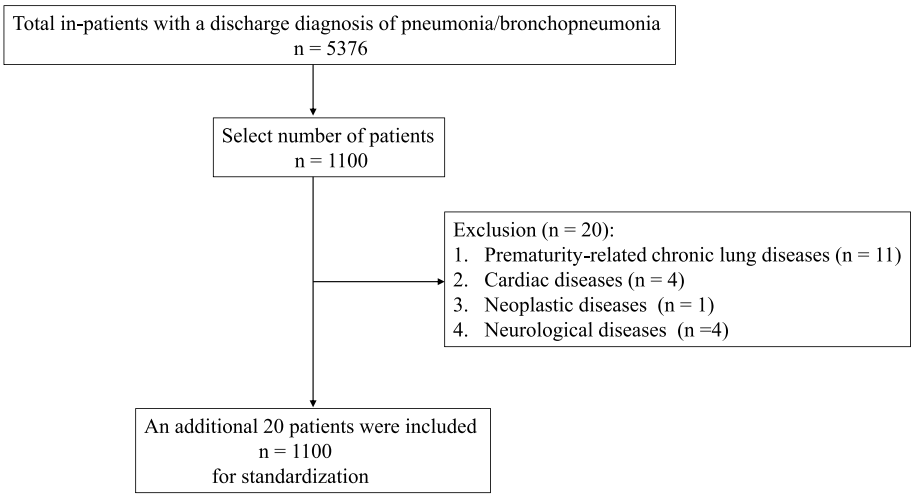


Fig. 1. Flow chart of study inclusion and exclusion process.

number of available hospital beds, we sampled different numbers of bronchopneumonia/pneumonia cases each year. We standardized this process by calculating the standardized ratio of the number of in-patients with a discharge diagnosis of pneumonia/bronchopneumonia (a) to the annual total of available hospital beds in a year (b), denoted as "z." The selected number of patients in a year (*n*) was determined by initially calculating the ratio of the standardized ratio for the current year to the sum of standardized ratios for past 11 years and then multiplying it by the sample size (1100 patients). After determining the number of patients for each year, cases were selected through stratified random sampling using a specific software RANDBETWEEN (Excel; Microsoft, Redmond, WA, USA).[15,16] The standardization formula for patient selection is shown below, and further details have been provided in Supplementary Materials 2 and 3.

$$n = \frac{\left(\frac{a}{b}\right)}{\Sigma\left(\frac{a}{b}\right)} \times 1,100 = \frac{z}{\Sigma z} \times 1,100$$

Detection of pathogens

Pathogens identified in the study were classified into four categories: (1) pneumococcus-related (*S. pneumoniae* detected as an isolated pathogen or in combination with other pathogens through blood culturing, PCR, or a urine antigen test, as described subsequently); (2) other bacteria (bacteria other than *S. pneumoniae* present with or without other coinfecting bacteria or virus); (3) virus (single or multiple viruses); and (4) unknown (no pathogen detected). Details of the pathogen groups are provided in Supplementary Material 1.

Bacterial examination

Bacteria were identified by culturing blood, pleural fluid, or bronchoalveolar lavage or performing PCR. To detect *S. pneumoniae* antigens, urine specimens were analyzed using the immunochromatographic Binax NOW test (Portland, Oregon, USA).[17] Group A *Streptococcus* (GAS) was confirmed by subjecting the collected pharyngeal swabs to culturing or rapid antigen detection test (RADT), specifically the BIOSYNEX® Strep A rapid immunochromatographic test (Fumouze Diagnostics, France), which qualitatively detects streptococcal antigens in oropharynx swabs.[18] *M. pneumoniae* was detected in nasopharyngeal swabs samples using PCR, which was performed following established protocols. The Meridian ImmunoCard Mycoplasma test, an enzyme immunoassay, was used to identify *M. pneumoniae* IgM antibodies. Additionally, *M. pneumoniae* IgG/IgM Antibody Test System (FTI-SERODIA-myco II test; Fujirebio Inc., Taipei, Taiwan) was used to test serum samples. Probable *M. pneumoniae* infections were defined as follows: (1) mycoplasma IgM seropositivity during the acute stage, (2) Detection of *M. pneumoniae* using PCR in a nasopharyngeal swab, or (3) a four time or more increase in mycoplasma IgG titer between the acute and convalescent stages.[19]

Viral examination

Nasopharyngeal swabs were subjected to viral testing. Rapid antigen direct tests (RADTs) were used to detect influenza A virus, influenza B virus, adenovirus, and respiratory syncytial virus (RSV). Other viruses were detected through virus culture or the multiplexed molecular assay FilmArray Respiratory Panel (RP; BioFire (™) Diagnostics, Inc., Salt Lake City, UT, USA) after its introduction to our laboratory in 2017. Information regarding the detected pathogens are provided in Supplementary Material 1.

Diagnosis of bronchopneumonia and pneumonia

Patients in the study were discharged with a diagnosis of pneumonia/bronchopneumonia. Bronchopneumonia and pneumonia were diagnosed by respective clinicians of each patient based on a general consensus: the presence of patchy centrilobular or peribronchial nodules indicated bronchopneumonia, whereas well-defined homogeneous consolidation of the lung parenchyma, with or without the air bronchogram sign, indicated pneumonia.[20]

Antibiotic groups and the assessment of antibiotic use

With the extensive implementation of the PCV13 vaccine, we predicted a potential decrease in antibiotic consumption. Therefore, we aimed to precisely measure and evaluate the change in antibiotic utilization. Antibiotics administered during the study period were categorized into five categories: (1) macrolides alone, which included roxithromycin, erythromycin, azithromycin, and clarithromycin; (2) first-line beta-lactam antibiotics alone, comprising penicillin G, ampicillin, amoxicillin/clavulanate, cefazolin, and cefuroxime; (3) macrolides administered in combination with first-line beta-lactam antibiotics; (4) other antibiotics or antiviral agents, such as cefotaxime, ceftriaxone, meropenem, vancomycin, levofloxacin, gentamicin, and oseltamivir; and (5) none, indicating cases where no antibiotics were used.

The antibiotic use was assessed based on two metrics: days of therapy (DOT) per patient-year and length of therapy (LOT) per patient-year, which provide an accurate estimate of polydrug therapy and therapy duration. DOT was defined as the number of days that each antimicrobial agent was prescribed to a patient, and LOT was defined as the duration of antimicrobial therapy, regardless of the number of used agents. The number of antibiotics used and the length of therapy were estimated using these metrics.[13,14]

Statistical analysis

All statistical analyses were performed using SPSS (version 26.0; IBM, Armonk, NY, USA). Continuous variables were analyzed using one-way analysis of variance. Categorical data were compared using the chi-squared test. Continuous data were presented as means, and categorical data were presented as absolute numbers or percentages. Pearson's correlation coefficient was used to examine the correlation between variables. A p value of <0.05 was considered to indicate statistical significance. Spearman's rank-order correlation coefficient, r_s, was used to present the strength and direction of the monotonic relationship between two variables.

Results

Prior to selecting cases from the pool of pneumonia/bronchopneumonia cases, we predetermined a suitable sample size of 1100. This was determined based on a type-I error of 0.05 and power of 80%, assuming a reduction in DOT for antibiotic use. The method for randomization is detailed in section study design. Of the selected cases, 20 were excluded as they didn't fit the inclusion criteria. To compensate for this exclusion, replacement selections were made using the same randomization method from the corresponding years of those omitted (Fig. 1).

Throughout the 11-year study period, the proportion of hospitalized patients with a discharge diagnosis of pneumonia or bronchopneumonia was approximately 1% of all hospitalized patients. The mean age was 21.89 ± 8.13 months. Most patients were 25–36 (n = 469, 43%) or 13–24 (n = 465, 42%) months of age, whereas 166 (15%) patients were 6–12 months of age. The overall cohort included 593 (54%) male and 507 (46%) female patients, with an identical sex distribution observed across the years ($p = 0.858$).

During the study period, 648 (59%) and 452 (41%) patients were discharged with a diagnosis of bronchopneumonia and pneumonia, respectively. There was no significant decline in the percentage of patients diagnosed with pneumonia over the years both before (N = 5376, $p = 0.152$) and after selection (N = 1100, $p = 0.166$). The mean hospital stay duration was 4.34 ± 1.99 days, which remained stable throughout the study period ($p = 0.163$) (Fig. 2A).

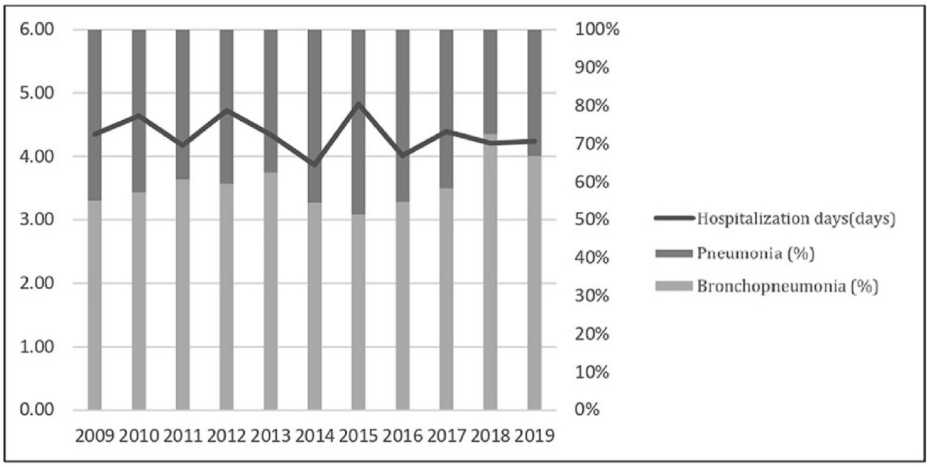
Laboratory tests conducted at admission included the measurement of WBC and absolute neutrophil counts and CRP level. The mean WBC, absolute neutrophil counts, and CRP level were 11.3 ± 5.3 × $10^3/\mu L$ (normal range: 6.0–14.0 × $10^3/\mu L$), 6072.4 ± 4410.4 mm^3, and 2.71 ± 4.19 mg/dL (normal range: 0.08–0.79 mg/dL), respectively. There were no statistically significant differences in WBC count ($p = 0.107$), absolute neutrophil count ($p = 0.246$), and CRP ($p = 0.381$) level during the study period (Fig. 2B).

In the studied 11 years, a definitive causative pathogen remained undetermined in 56% patients. Meanwhile, 37% patients presented with either a singular or multiple viral infections, and *S. pneumoniae* was identified as either a sole pathogen or copathogen in 4% patients. Mixed infections with bacteria other than *S. pneumoniae* accounted for 3% all cases. Despite yearly variations in test methods and testing rates, no significant shift in the detection rate of *S. pneumoniae* among hospitalized patients was observed throughout the study period ($p = 0.166$). Conversely, the number of cases with indeterminate pathogens exhibited a downward trend over time ($r^2 = 0.204$, $r_s = -0.165$, $p < 0.05$). This is likely attributed to the annual increase in the number of cases where viral infections were detected ($r^2 = 0.176$, $r_s = 0.101$, $p < 0.05$). Supplementary material 4 depicts the annual ratios of pathogens detected in the study cohort.

Overall, 59% patients were administered monotherapy with first-line beta-lactam antibiotics. In our study, 30% of patients received combination therapy with macrolides and first-line beta-lactam antibiotics. Only 4% were treated exclusively with macrolides, and an additional 4% were given macrolides alongside other antibiotics. Only 3% of the patients were not treated with antibiotics. The annual distribution of specific antibiotics used for treatment is shown in Fig. 3A. An analysis of the yearly variations in the utilization of macrolides and first-line beta-lactam antibiotics over the 11-year study duration indicated a notable escalation in the proportion of macrolide prescriptions ($r^2 = 0.546$, $r_s = 0.031$, $p = 0.009$) (Fig. 3B). Conversely, the trend in the usage of first-line beta-lactam antibiotics remained relatively constant throughout the study period ($r^2 = 0.1738$, $r_s = -0.177$, $p = 0.202$) (Supplementary Material 5).

The mean DOT and LOT were 5.15 and 4.04 per patient-year, respectively. Over the span of 11-year study period, no statistically significant changes were observed in the DOT or LOT per patient-year ($r^2 = 0.1698$, $r_s = 0.076$, $p = 0.208$ and $r^2 = 0.0444$, $r_s = -0.027$, $p = 0.534$, respectively) (Fig. 4). The DOT and LOT analyses were further divided into several subgroups based on the types of commonly used antibiotics and antibiotic use for viral pneumonia. In the macrolide-only

(A) Annual distribution of diagnoses and average length of hospital stay



(B) Annual changes in mean white blood cell count (WBC), absolute neutrophil count, and C-reactive protein (CRP) during the study period

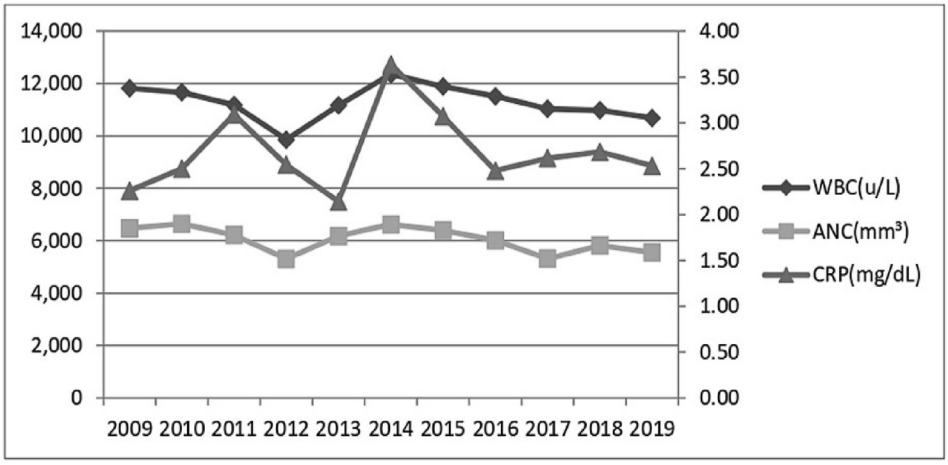


Fig. 2. (A) Annual distribution of diagnoses and average length of hospital stay. (B) Annual changes in mean white blood cell count (WBC), absolute neutrophil count, and C-reactive protein (CRP) during the study period.

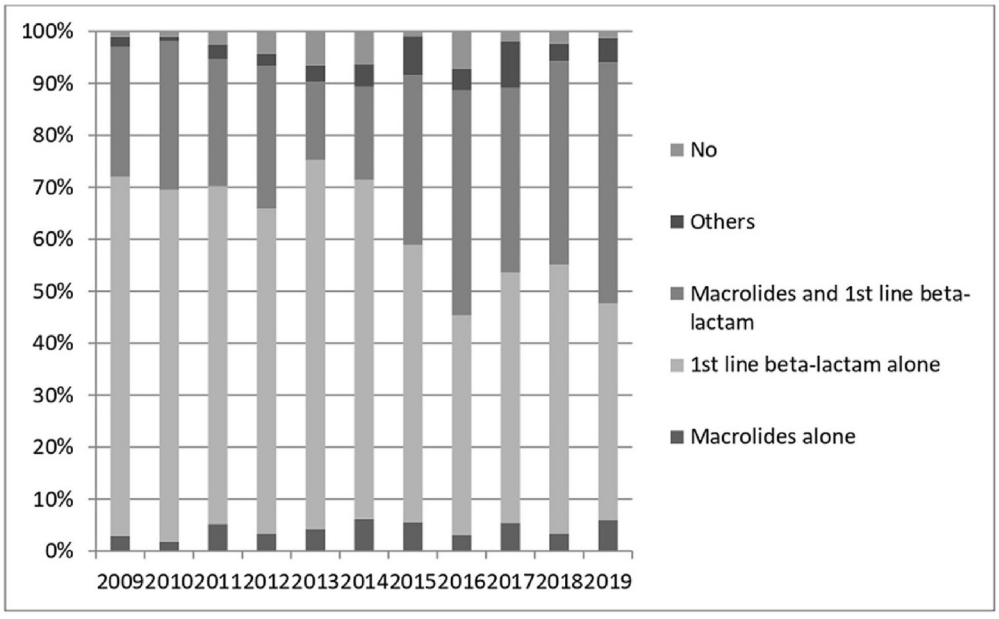
group, the mean DOT and LOT were 2.86 and 2.96 per patient-year, respectively. Throughout the study duration, no significant statistical changes were observed ($r_s = -0.112$, $p = 0.787$ and $r_s = -0.072$, $p = 0.398$, respectively) (Supplementary Material 6). The DOT and LOT of patients who were only prescribed first-line beta-lactam were 4.03 and 3.97 per patient-year, respectively, and neither of these values exhibited a decline throughout the study ($r_s = -0.100$, $p = 0.050$ and $r_s = -0.096$, p = 0.058) (Supplementary Material 7). In the group receiving a combination of macrolides and first-line beta-lactam antibiotics, the DOT and LOT were 7.67 and 4.39 per patient-year, respectively, and LOT increased throughout the study period ($r_s = 0.333$, $p = 0.028$) (Supplementary Material 8). There was no overall decline in the utilization of single or combined antibiotic regimens.

Regarding the antibiotic usage in cases of viral pneumonia, the DOT and LOT were slightly higher than the overall averages at 5.54 and 4.41 per patient-year, respectively. No statistically significant changes were observed throughout the study period ($r_s = -0.006$, $p = 0.787$ and $r_s = -0.156$, $p = 0.398$, respectively) (Supplementary Material 9).

Discussion

In our longitudinal study conducted over a period of 11 years, we discovered that the extensive distribution of the PCV13 vaccine did not result in the expected decrease in antibiotic usage among hospitalized pediatric patients with pneumonia. In a systematic literature review published in

(A) Annual distribution of administered antibiotics



(B) Scatter plot showing the increased annual percentage of patients using macrolides during the study period

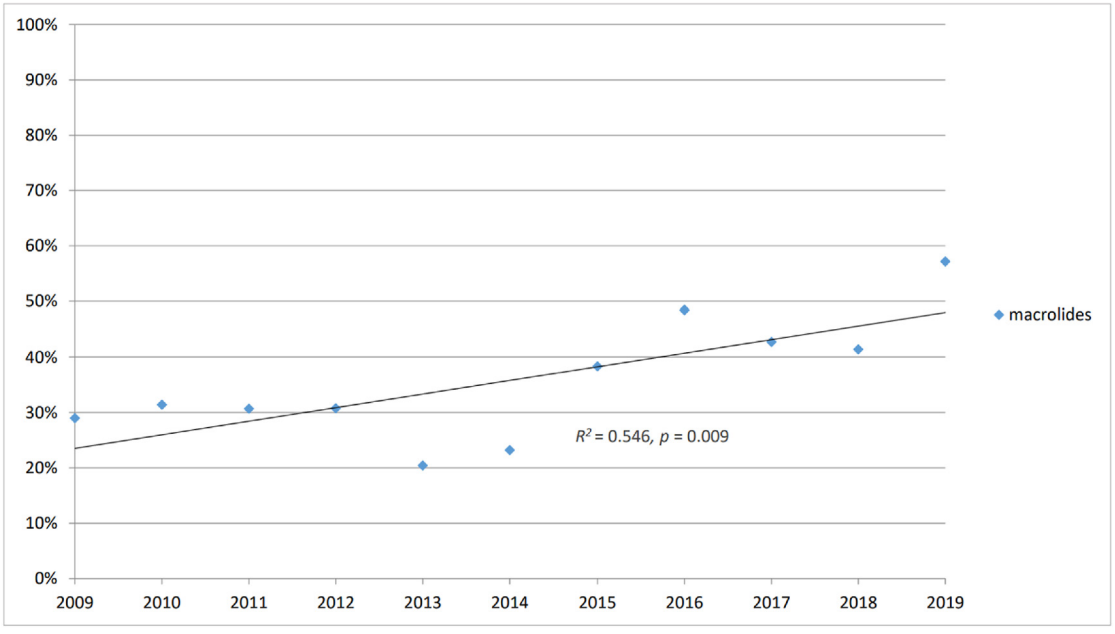
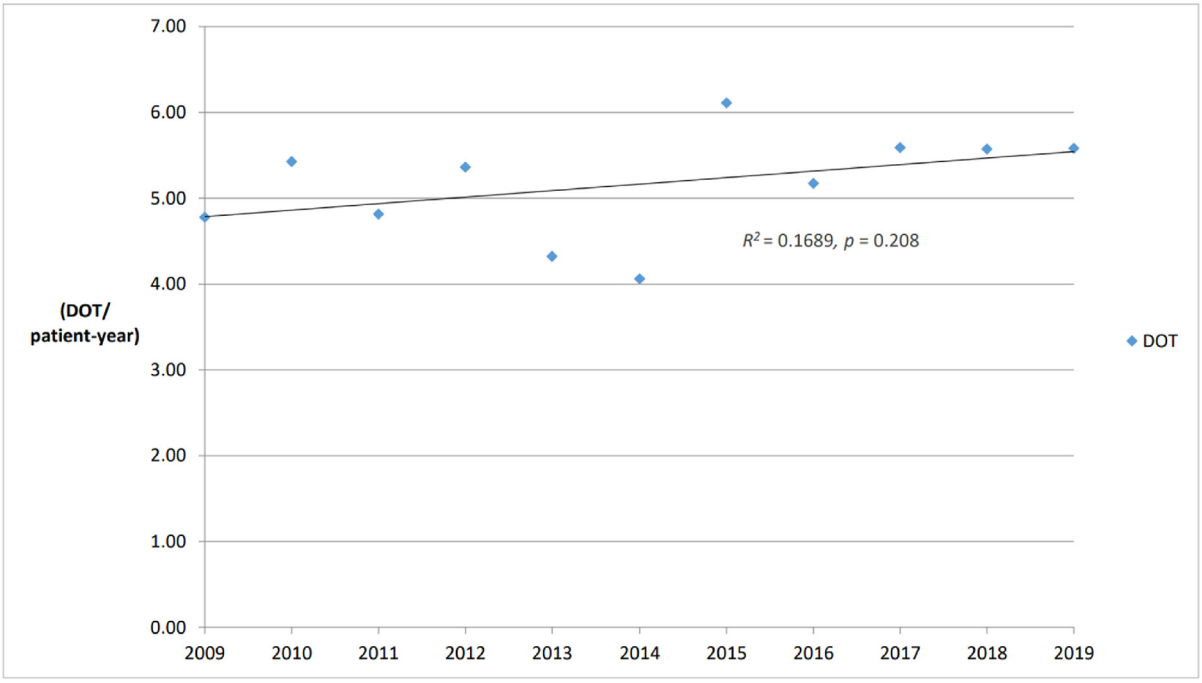


Fig. 3. (A) Annual distribution of administered antibiotics. (B) Scatter plot showing the increased annual percentage of patients using macrolides during the study period.

(A) Scatter plot showing the days of therapy (DOT) per patient-year



(B) Scatter plot showing the length of therapy (LOT) per patient-year

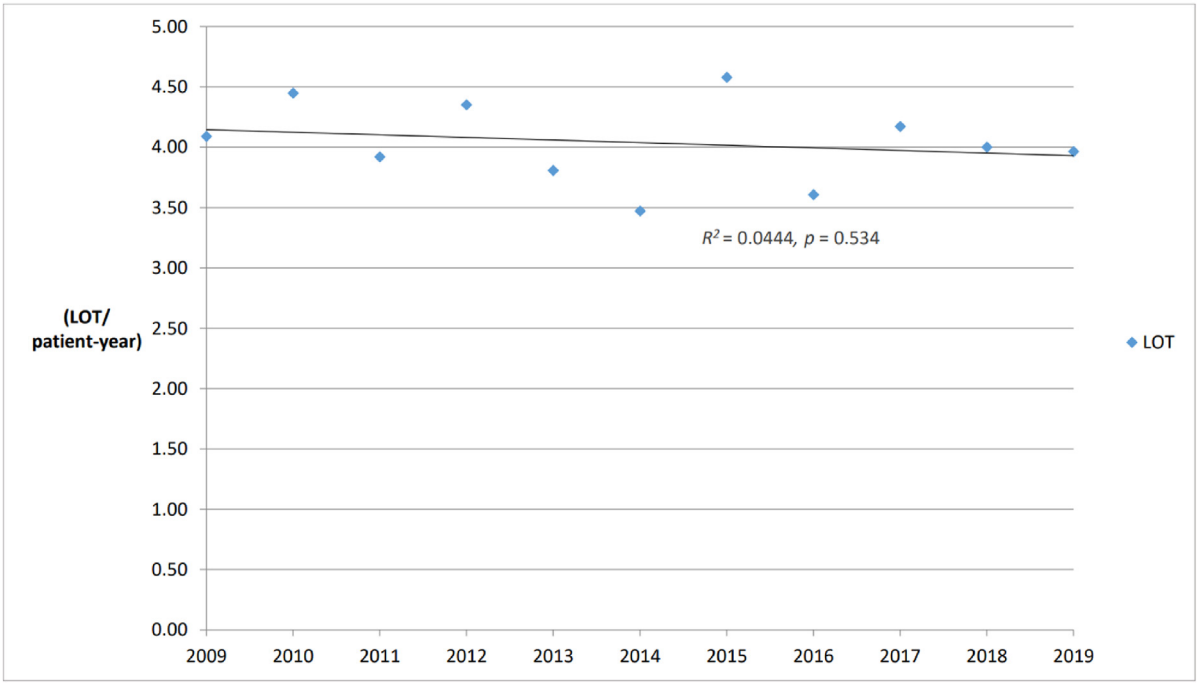


Fig. 4. (A) Scatter plot showing the days of therapy (DOT) per patient-year. (B) Scatter plot showing the length of therapy (LOT) per patient-year.

2020 that analyzed studies from England, France, the Netherlands, Denmark, and Iceland revealed that 12 out of the 13 studies reported a significant reduction in the use of antimicrobial following vaccination.[11] Of these studies, five investigated the impact of antibiotic use following PCV13 vaccination, whereas the other eight studies investigated the use of antibiotics after the introduction of other vaccines such as PCV7 vaccine, the 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10), and the 23-valent nonconjugated vaccine.[11] Despite the apparent decline in overall use of antibiotics, the bulk of this decrease is associated more with the management of acute otitis media than with the treatment of pneumonia.[11]

Concerning the selection of prescribed antibiotics, we noted an annual escalation in the proportion of patients exclusively using macrolides. Despite the fact that the incidence of probable Mycoplasma infections did not notably increase in our study, the pattern of using only macrolide persisted and even exhibited an ascending tendency. The potential overuse of macrolides in the treatment of patients with pneumonia is not an anomaly exclusive to our study. A retrospective cohort investigation in the United States, scrutinizing antibiotic treatment patterns in outpatient children with community-acquired pneumonia, revealed that macrolide monotherapy was the predominant antibiotic approach and was used in 43.2% patients. It was reported that the rate of macrolide usage far exceeded the estimated point prevalence of atypical pathogens in pediatric community-acquired pneumonia, which ranged from 8% to 14%.[21] Similarly, several retrospective studies from various countries have revealed a mismatch between clinical guidelines and actual patient management, leading to antibiotic overuse and a rise in antibiotic-resistant community-acquired pathogens including macrolide resistant *M. pneumoniae* in recent years.[22,23] In Taiwan, the rate of macrolide resistance in patients infected with *M. pneumoniae* was >70% after 2017.[24] Persistence of the current trends in antibiotic use is expected to increase the prevalence of macrolide-resistant *M. pneumoniae*.

The incidence of IPD in children after PCV13 introduction has declined.[9,25] In contrast, our findings indicate a stable trend in the prevalence of discharge diagnosis of pneumonia or bronchopneumonia in the years after PCV13 introduction in 2015; in particular, there was no observable annual reduction in WBC counts or CRP levels. This discrepancy between our study and previous investigations may be attributed to differences in disease severities. In contrast to earlier investigations that have concentrated on the patterns associated with IPD, this study did not specifically isolate and examine data of patients hospitalized in the intensive care unit or those exhibiting severe clinical conditions. Another concern is that the discharge diagnosis of pneumonia and bronchopneumonia was based on the results of chest X-rays, which could potentially lead to subjective discrepancies in the interpretation among clinical practitioners, thus resulting in an overdiagnosis of pneumonia.

In our study, we identified viral infections in 37% of the patients, making it the predominant category of detected pathogens. A systematic review[26] and several studies based in the United Kingdom, United States, and low- and middle-income countries[27—30] have revealed the significant role of viruses in children hospitalized with community-acquired pneumonia, especially in regions with high pneumococcal conjugate vaccine coverage. Similar results have been reported in a study in Taiwan.[10] Despite the high prevalence of viral pneumonia, 97% hospitalized patients were administered antibiotic treatment. Additionally, we observed no discernible variations in the DOT and LOT in patients with viral pneumonia. The total antibiotic use did not decrease despite the launch of the pneumococcal vaccination campaign, which is a counterintuitive situation in a country with a high vaccine completion rate.

Throughout the study period, there were no significant changes observed in the detection of *S. pneumoniae* among the hospitalized patients. The possible reason is that following PCV13 administration, a serotype replacement from vaccination serotypes to nonvaccine serotypes occurred within pneumococcal nasopharyngeal colonization. This resulted in the sustained global colonization of *S. pneumoniae* by nonvaccine serotypes.[31,32] Another possible reason for the limited decline in *S. pneumoniae* detection could be attributed to the increased utilization of diagnostic methods, such as the urine pneumococcal antigen test, over the course of these 11 years.

Our study has several limitations. First, this was a single-center study with a relatively limited number of participants, the sample size varied over the years, and not all hospitalized patients were included in the study. However, the optimal sample size with an adequate power was calculated to detect statistical significant changes. Second, we specifically selected patients aged 6 months up to 3 years because the highest incidence of IPD in children has been observed in patients in Taiwan aged 2—4 years,[33,34] whereas it is detected among children younger than 2 years worldwide.[35] Moreover, we decided to focus on the younger age groups, as they appear to be more susceptible to IPD in Western countries, albeit this pattern is not observed in Taiwan. Importantly, children within this age should not be subject to excessive antibiotic usage. Third, despite our meticulous collection of patient data encompassing detailed radiologic and laboratory tests for precise diagnosis, the potential for uncontrolled residual confounding persists due to the retrospective nature of our study design. For instance, the discharge diagnosis of pneumonia and bronchopneumonia was reliant on the results of chest X-rays, which might lead to an overdiagnosis of pneumonia due to the subjective interpretation that may vary among clinical practitioners. Lastly, not all patients were evaluated for additional pathogens, which might have led to the over- or underestimation of the prevalence of bacterial and viral infections. For example, the rapid assay for the detection of *S. pneumoniae* urinary antigen is highly sensitive but not sufficient to distinguish between patients suffering from pneumococcal disease and those merely hosting *S. pneumoniae* colonization,[36] thus resulting in an overestimation of pneumococcus-related pneumonia cases in the present study.

Conclusions

In summary, following the introduction of PCV13 in Taiwan, our study has not observed a decrease in antibiotic use

among children aged 6 months—3 years who were discharged with a diagnosis of pneumonia or bronchopneumonia. It is of utmost importance to focus on improving treatment accuracy and reducing unnecessary antibiotic consumption as strategic measures to prevent the possibility of antibiotic resistance and other associated adverse effects.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.09.001.