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Impact of pneumococcal conjugate vaccination on hospitalized childhood pneumonia in Taiwan

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BACKGROUND: A national 13-valent pneumococcal conjugate vaccine (PCV13) catch-up program among children aged 2–5 years in 2013, before routine infant immunization in 2015, successfully reduced serotype 19A-related invasive pneumococcal diseases in Taiwan. We aimed to investigate its impact on hospitalized childhood pneumonia.
METHODS: We analyzed the National Health Insurance Research Database, 2001–2017, for hospitalized children aged <18 years with the diagnoses of all-cause pneumonia, lobar/pneumococcal pneumonia, and pneumococcal parapneumonic diseases. The study period was divided into 2001–2005 (pre-PCV), 2006–2012 (private sectors), and 2013–2017 (universal PCV13 vaccination).
RESULTS: On pneumococcal parapneumonic diseases, the national PCV13 vaccination program was associated with an immediate decline in 2–4-year-old children and significant decreasing trends in all ages. The incidence rate ratios of 2016–2017/2011–2012 were 0.16 (95% confidence interval [CI], 0.06–0.40) and 0.18 (95% CI, 0.13–0.23) in children aged < 2 and 2–4 years, respectively. We observed an increase of lobar/pneumococcal pneumonia cases after an early decline. The intensive/invasive medical needs and the fatality of all-cause pneumonia decreased significantly in children of all ages.
CONCLUSIONS: Pneumococcal parapneumonic diseases and the disease burden of lobar/pneumococcal pneumonia and lower respiratory tract infections declined after the national PCV13 vaccination program.

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IMPACT:

- The impact study of the PCV13 immunization program on childhood pneumonia in Asian countries remained limited.
- The unique PCV13 immunization program in Taiwan, catch-up before primary infantile series, reduced severe childhood pneumococcal pneumonia at 5 years post PCV13.
- The intensive and invasive medical needs and fatality of all-cause pneumonia decreased significantly in children of all ages.
- We observed an increase in lobar/pneumococcal pneumonia after an early decline.

INTRODUCTION

The introduction of pneumococcal (PnC) conjugate vaccines (PCVs) has reshaped the epidemiology of childhood PnC diseases. Regardless of different schedules, the direct and indirect impact of universal PCV vaccination programs on both invasive PnC disease (IPD) and non-IPD, such as non-bacteremic pneumonia and otitis media, has been well documented in the United States, the United Kingdom, and Australia.[1–3] The impact was subject to the influence of serotype distribution, vaccine coverage, and surveillance system in different countries. Serotype replacement could erode the success of the PCV vaccination program and has been the focus of public health.[4] Replacement disease caused by serotype 19A has been noted in countries where 7-valent PCV (PCV7) was introduced.[5] Broader protection from PCVs with higher-valency, 10-valent PCV (PCV10) and 13-valent PCV (PCV13), further reduced PnC disease burden in children.[6]

The PCV7, PCV10, and PCV13 were licensed in Taiwan in 2005, 2010, and 2011, respectively (Fig. 1). The uptake rates increased gradually in the private sector.[7,8] Public-funded immunization programs were provided to high-risk groups since 2009. In contrast to most countries where children < 2 years had the highest IPD incidence, the age group with the highest IPD incidence rate in Taiwan was children aged 2–4 years.[9] The epidemiology of childhood lobar/PnC pneumonia and empyema in Taiwan also showed that children aged 2–4 years had the highest incidence rates.[10] The introduction of PCV7 was followed by infections caused by the replacement serotypes since 2007, with the emergence of highly invasive serotype 19A.[5,11] The increasing cases of complicated pneumonia and empyema related to serotype 19A in children aged 2–4 years in 2011–2012 prompted a national PCV13 catch-up program in 2013–2014 and primary PCV13 infant immunization (2 + 1) since 2015, which successfully reduced IPD incidence rate, especially serotype 19A, in children < 5 years.[12]

Pneumonia is the leading infectious cause of childhood mortality and morbidity worldwide. As the World Health

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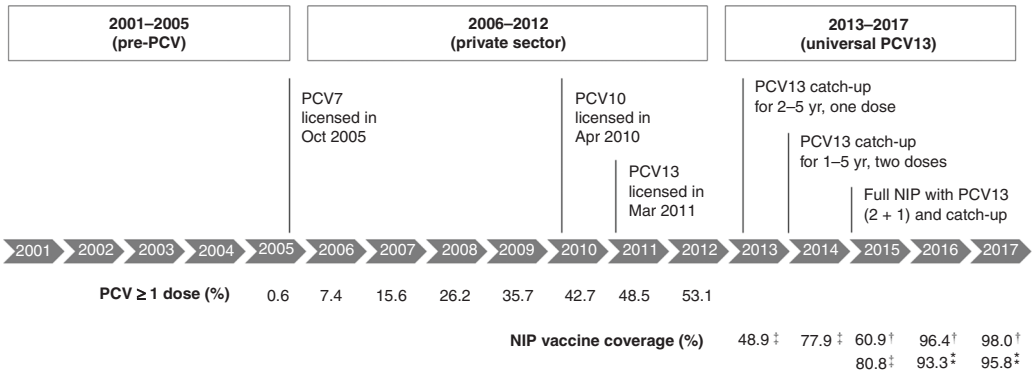

Fig. 1 Timeline of PCV licensure and uptake rates before and after PCV national immunization program in Taiwan. ‡Catch-up, one dose of PCV13 for children aged 2–5 years since March 2013 and expanded to children between 1 and 2 year(s) since January 2014 (1 + 1). †Primary series, two doses of PCV13 for infants aged 2 and 4 months since January 2015; ⁑Booster, one dose of PCV13 after completion of primary series (2 + 1). *NIP* National Immunization Program, *PCV* pneumococcal conjugate vaccine.

Organization estimated, pneumonia was associated with 15% of deaths in children < 5 years in 2017.[13] In the Global Burden of Diseases report in 2015, PnC pneumonia alone accounted for 55.8% of lower respiratory tract infection (LRTI) mortality in children < 5 years globally.[14] Before PCV introduction in Taiwan, about 40% of hospitalized pediatric community-acquired pneumonia (CAP) in 2001–2002 was PnC related.[15] Until 2012–2015, *Streptococcus pneumoniae* remained the causal agent for at least 30% of hospitalized CAP in children.[16] Few studies explored the long-term impact of PCVs on non-IPDs, such as pneumonia, so we aimed to investigate the impact of PCVs on the trend of childhood pneumonia in Taiwan between 2001 and 2017, with emphasis on 5 years after the implementation of the national PCV13 immunization program.

MATERIALS AND METHODS

Setting and data source

National Health Insurance (NHI) program has been implemented in Taiwan since 1995. The NHI Research Database was established by Taiwan's Ministry of Health and Welfare (MOHW) and claims that the registry files of the beneficiaries include data of outpatient visits, hospital admissions, prescriptions, diseases, and vital status of > 99% of the 23 million population in Taiwan.[17] The data used in our retrospective study were de-identified and were obtained through a formal application to the Health and Welfare Data Science Center at the MOHW. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee.

Study population

The data of hospitalized children < 18 years with the discharge diagnoses of pneumonia were retrieved from January 2001 to December 2017. The coded diagnoses were defined by the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) before 2015 and ICD-10 from 2016 (Supplementary Table S1). Lobar/PnC pneumonia, parapneumonic empyema, and pleural effusion were identified with the specific codes. We included all-listed diagnoses and episodes for analysis. The episodes from infants aged < 1 month were excluded to avoid perinatal pneumonia.

Outcome measurement

The primary outcome was to describe and compare the trends of annual incidence rates of all-cause pneumonia, lobar/PnC pneumonia, and parapneumonic diseases within the study period (Fig. 1), which was divided into 2001–2005 (pre-PCV), 2006–2012 (PCVs in the private sectors), and 2013–2017 (universal PCV13). The vaccine coverage data were derived from the estimation by Taiwan Centers for Disease Control,[7,8] which had full access to the National Immunization Information System. The private sectors, with an estimated 93% included in the NHI program,[16] referred to the hospitals and clinics where parents or guardians took children for PCV vaccination at their own expense. The secondary outcome was to evaluate intensive or invasive in-hospital treatment concerning the requirement of intensive care, the need for mechanical ventilation, surgical procedures, and in-hospital deaths. Children were grouped according to ages (years): under 2, 2–4, and 5–17.

Validation cohort

To validate the reliability of the coded diagnoses, we established a cohort from the integrated Medical Database of the National Taiwan University Hospital, a 2127-bed tertiary care center in Taiwan. The medical records with the discharged diagnosis of PnC pneumonia with parapneumonic diseases from 2008 to 2017 were reviewed. The diagnosis was validated in 55 of the 56 medical records, with a positive predicted value of 98%.

Statistical analysis

The incidence of pneumonia was calculated as a rate per 100,000 children at risk per year by dividing the annual episodes of pneumonia by the age-specific, mid-year population of children as reported between 2001 and 2017 from the Taiwan census data. The incidence rate of all-cause hospitalization was also calculated. We used χ^2 tests to compare the difference of the proportion of different outcomes between the age groups and periods. The incidence rate ratios (IRRs) between different years, with 95% confidence intervals (CIs) were calculated.

We adopted interrupted time-series analyses with pneumonia (all-cause pneumonia and lobar/PnC with and without parapneumonic diseases) admission rates as the main outcomes. The segmented regression with autoregressive error model was used to compare the trends of pneumonia within the study periods in respective age groups.[18] The time unit chosen was quarter because of significant seasonal fluctuation of pneumonia outcomes and in order to fit the model better. We performed stepwise autoregression with an initial order of 5 (quarterly data) to select the order of the autoregressive error model. The quarter was defined as spring (from February to April), summer (May to July), autumn (August to October), and winter (November to January). The intervention assessment of PCV7 introduction and universal PCV13 was estimated and reported as the immediate effects and long-term trends.

The logistic regression model was used to evaluate the need for in-hospital treatment and deaths with the adjustment of age, sex, area, and season in respective periods. Odds ratios with 95% CIs were calculated.

The IRR was considered significant when the 95% CI was not including the value of 1. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Data management and statistical analysis were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Overview of hospitalized childhood pneumonia in Taiwan

We analyzed the nationwide population-based episodes of hospitalization for all-cause and lobar/PnC pneumonia and parapneumonic diseases in children aged < 18 years in 2001–2017. Among 5,672,230 all-cause hospitalizations (Supplementary Fig. S1) in the

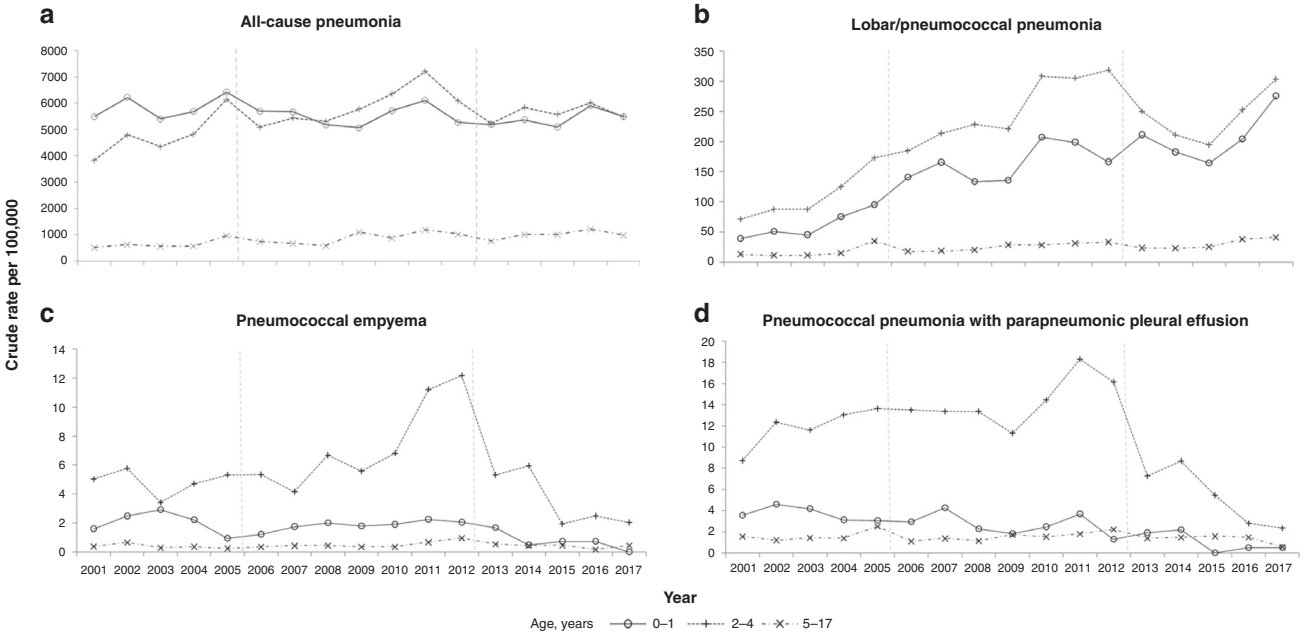

Fig. 2 Age-specific incidence rates of childhood pneumonia in the study period. Annual incidence of (**a**) all-cause pneumonia, (**b**) lobar/pneumococcal pneumonia, (**c**) pneumococcal empyema, and (**d**) pneumococcal pneumonia with parapneumonic pleural effusion in children aged one month to < 18 years, 2001–2017. The dashed lines indicate each of the vaccine eras.

study period, a total of 1,554,559 (27%) episodes met the definition of all-cause pneumonia. Figure 2 shows annual incidence rates of all-cause pneumonia, and different types of pneumonia in children of different ages, 2001–2017. The demographic characteristics showed a male predominance of all-cause pneumonia in all age groups (Supplementary Table S2). The proportion of lobar/PnC pneumonia and PnC septicemia among all-cause pneumonia was greater in children aged 2–4 years ($p < 0.001$) as compared to that in other age groups. Children with lobar/PnC diseases tended to have a longer length of stay than those with all-cause pneumonia. Parapneumonic empyema, more often in children > 2 years, was coded in 0.2% of all-cause pneumonia. Pleural effusion was noted in 0.2%, 0.63%, and 1.05% among children aged < 2, 2–4, and 5–17 years, respectively. The parapneumonic diseases were associated with lengthy hospitalization for a median of at least 14 days. Nearly 5% of children aged < 2 years required intensive care. About 1% of children < 2 years received mechanical ventilation. Surgical procedures were performed in 0.2% of cases, mainly in children > 2 years. In-hospital death rates were greater in children aged < 2 and 5–17 years (0.18% and 0.22%, respectively) than those in other age groups.

Despite the introduction of PCVs, the proportion of lobar/PnC pneumonia increased in all ages and remained 3–4% of all-cause pneumonia after universal PCV13 vaccination in 2013–2017 (Supplementary Table S2). The proportion of parapneumonic diseases decreased in all ages since the introduction of PCVs in the private sectors in 2006–2012 ($p < 0.001$) and declined further with universal PCV13 vaccination in 2013–2017 ($p < 0.001$). With the uptake rates of PCVs increased, the requirement for intensive care, mechanical ventilation and surgical procedures, and in-hospital death rates decreased in all ages. Figure 2c, d show a sharp decline in the annual incidence rates of severe pneumonia including PnC empyema and PnC pneumonia with parapneumonic pleural effusion after universal PCV13 vaccination in 2013, especially among 2–4-year-old children.

Trend before PCV introduction (2001–2005)

Based on time-series model estimation, the trend for all-cause pneumonia incidence increased significantly in children aged 2–4 years ($p = 0.016$) and 5–17 years ($p = 0.015$) before the introduction of PCV7 in late 2005 (Table 1 and Fig. 3a). The trend was similar for all-cause pneumonia as primary, secondary, or any diagnosis (data not shown). The trend for lobar/PnC pneumonia incidence also significantly increased in children aged 2–4 years ($p = 0.001$) and 5–17 years ($p < 0.0001$) (Table 1 and Fig. 3b). There was no significant trend for PnC parapneumonic diseases incidence except a significant trend of increase in children aged 5–17 years ($p = 0.021$) (Table 1 and Fig. 3c).

Trend after PCV in the private sectors (2006–2012)

Following the introduction of PCV7, there was a significant and immediate decrease of all-cause pneumonia ($p = 0.028$), lobar/PnC pneumonia ($p = 0.0001$), and PnC parapneumonic diseases ($p = 0.0003$) in 5–17-year-old children or adolescents (Table 1 and Fig. 3). We observed no significant trend for all outcomes in children of all ages in 2006–2012.

Trend after universal PCV13 immunization (2013–2017)

Following the national PCV13 catch-up program in children aged 2–5 years, there was a significant and immediate decline of lobar/PnC pneumonia ($p < 0.0001$) and PnC parapneumonic diseases ($p = 0.0003$) in children aged 2–4 years, and all-cause pneumonia ($p = 0.013$) and lobar/PnC pneumonia ($p < 0.0001$) in children aged 5–17 (Table 1 and Fig. 3). With the primary infant vaccination program (2 + 1) launched in 2015, the trend for PnC parapneumonic diseases further declined in children aged < 2 years ($p = 0.013$), 2–4 years ($p < 0.0001$), and 5–17 years ($p < 0.0001$) (Table 1 and Fig. 3c). The sharp decline for PnC parapneumonic diseases was most obvious in children aged < 5 years with more than 80% reduction in 2016–2017 as compared to 2011–2012 (Table 2 and Fig. 3c).

In the first 3 years (2013–2015) of the universal PCV13 program, there was a significantly decreasing trend of lobar/PnC pneumonia in children aged < 2 years ($p = 0.004$) and 2–4 years ($p = 0.0001$) (Supplementary Table S3), but no significant trend was observed after combining 2016–2017 (Table 1). A modest (25–35%) decline of lobar/PnC pneumonia in children aged >2 years was noted in 2014–2015 as compared to 2011–2012 (Table 2). A phenomenal (37–64%) rebound was seen for all ages

Table 1. Interrupted time series with a segmented regression model for seasonal incidence rates of childhood pneumonia outcomes, 2001–2017.

	2001–2005		2006–2012				2013–2017					
	Trend		Immediate[a]		Trend[b]		Immediate[c]		Trend[d]			
Age (years)	Estimated change	*P* value	Estimated change	*P* value	Estimated change	*P* value	Estimated change	*P* value	Estimated change	*P* value		
All-cause pneumonia												
<2	6.39	0.46	−151.01	0.24	−6.69	0.51	−60.01	0.64	4.50	0.66		
2–4	28.45	0.016	−239.00	0.15	−12.95	0.37	−257.15	0.13	−16.22	0.26		
5–17	5.35	0.015	−71.63	0.028	0.23	0.92	−83.22	0.013	−2.03	0.40		
Lobar/pneumococcal pneumonia												
<2	0.90	0.12	11.07	0.12	−0.71	0.34	10.00	0.172	0.21	0.77		
2–4	1.58	0.001	−0.83	0.89	−0.20	0.74	−26.13	<0.0001	−0.59	0.33		
5–17	0.31	<0.0001	−3.58	0.0001	−0.11	0.10	−4.81	<0.0001	0.12	0.08		
Pneumococcal empyema[e]												
<2	−0.015	0.26	−0.006	0.98	0.010	0.47	−0.048	0.81	−0.038	0.013		
2–4	0.069	0.11	−0.926	0.14	0.024	0.63	−2.477	0.0003	−0.251	<0.0001		
5–17	0.012	0.021	−0.292	0.0003	0.002	0.72	−0.153	0.06	−0.025	<0.0001		

PCV pneumococcal conjugate vaccine.
Immediate change refers to the change within one-quarter (season) after [a]PCV7 licensure or [c]universal PCV13 vaccination. A trend is a progressively quarterly change in the slopes of the outcomes after [c]PCV7 licensure or [d]universal PCV13 vaccination. [a,b]Comparison to years of 2001–2005; [c,d]comparison to years of 2006–2012. [e]Pneumococcal pneumonia with parapneumonic pleural effusion was also included in the analyses. All rate changes were per 100,000 quarterly.

in 2016–2017, which was supported by an increase of lobar/PnC pneumonia with PnC septicemia in the same period (Supplementary Fig. S2). We observed no significant trend for all-cause pneumonia for all ages in 2013–2017 (Fig. 3a).

Impact of PCV on intensive and invasive in-hospital treatment

We defined LRTI as all-cause pneumonia except for lobar/PnC pneumonia. By the logistic regression model analyses (Table 3), children with LRTI and lobar/PnC pneumonia in 2013–2017 (post PCV13) were associated with significantly less need for intensive care, mechanical ventilation, and surgical procedures and in-hospital deaths in all ages compared with those in 2006–2012 (private sectors).

Children aged 2–4 years with PnC empyema in 2013–2017 (post PCV13) were associated with significantly less need for intensive care and surgical procedures compared with those in 2006–2012 (private sectors) (Table 3). Only one fatal case in children aged <2, eight fatal cases in children aged 2–4, and none in those aged 5–17 with PnC empyema, so logistic regression was not feasible for in-hospital death related to PnC empyema.

Children of all ages with LRTI and lobar/PnC pneumonia in 2013–2017 (post PCV13) were associated with decreased intensive and invasive medical needs and deaths as compared with those in 2001–2005 (pre-PCV7). The association was similar for children of all ages in 2006–2012 (private sectors) but to a lesser degree (Supplementary Table S4).

DISCUSSION

This nationwide population-based study was the first and most comprehensive investigation of hospitalized childhood pneumonia before and after PCV introduction in Taiwan. Our data showed an immediate decline and significant decreasing trend of severe pneumonia with parapneumonic diseases, especially in children aged 2–4 years, at 5 years after the implementation of the national PCV13 immunization program, and the intensive and invasive medical needs related to all-cause pneumonia significantly decreased in all ages. The trend for lobar/PnC pneumonia was significantly decreasing in the first 3 years (2013–2015) of PCV13 implementation, but increased in the past 2 years of the study (2016–2017), thus offsetting the overall trend.

Our analysis confirmed the decline of severe PnC pneumonia both in children < 5 years and 5–17 years, indicating a significant herd effect. The annual rates of PnC parapneumonic diseases in children of all ages in the post-PCV13 era were significantly lower compared with the pre-PCV7 era. Several studies have demonstrated earlier and greater impact of PCV13 on empyema[19,20] than that on pneumonia.[21] A recent study in Taiwan also found a 72% decrease in pediatric PnC empyema admissions among children aged 2–5 years after the PCV13 implementation and the effect remained substantial at 4 years post PCV13.[22] Since the rebound of PnC empyema had been reported previously,[23] prospective surveillance should be continued.

Although the overall post-PCV13 trend for lobar/PnC pneumonia was not significantly decreasing in our study, the disease morbidity and mortality were significantly reduced as compared with 2006–2012 (private sectors) and 2001–2005 (pre-PCV), shown in Table 3. An earlier study 4 years after PCV13 introduction in the United States identified no change of disease burden, despite a significant decrease in pediatric hospitalization rates of all and complicated PnC pneumonia cases.[24] Another French study showed a significant decrease of severe pneumonia 7 years post PCV13, but a slight and significant increase in all CAP was observed.[25] We speculated the interaction of host factors, disease pathogenesis, invasiveness of carriage serotypes, serotype replacement, and vaccination schedules may reshape the landscape of childhood pneumonia in the post-PCV13 era.[26]

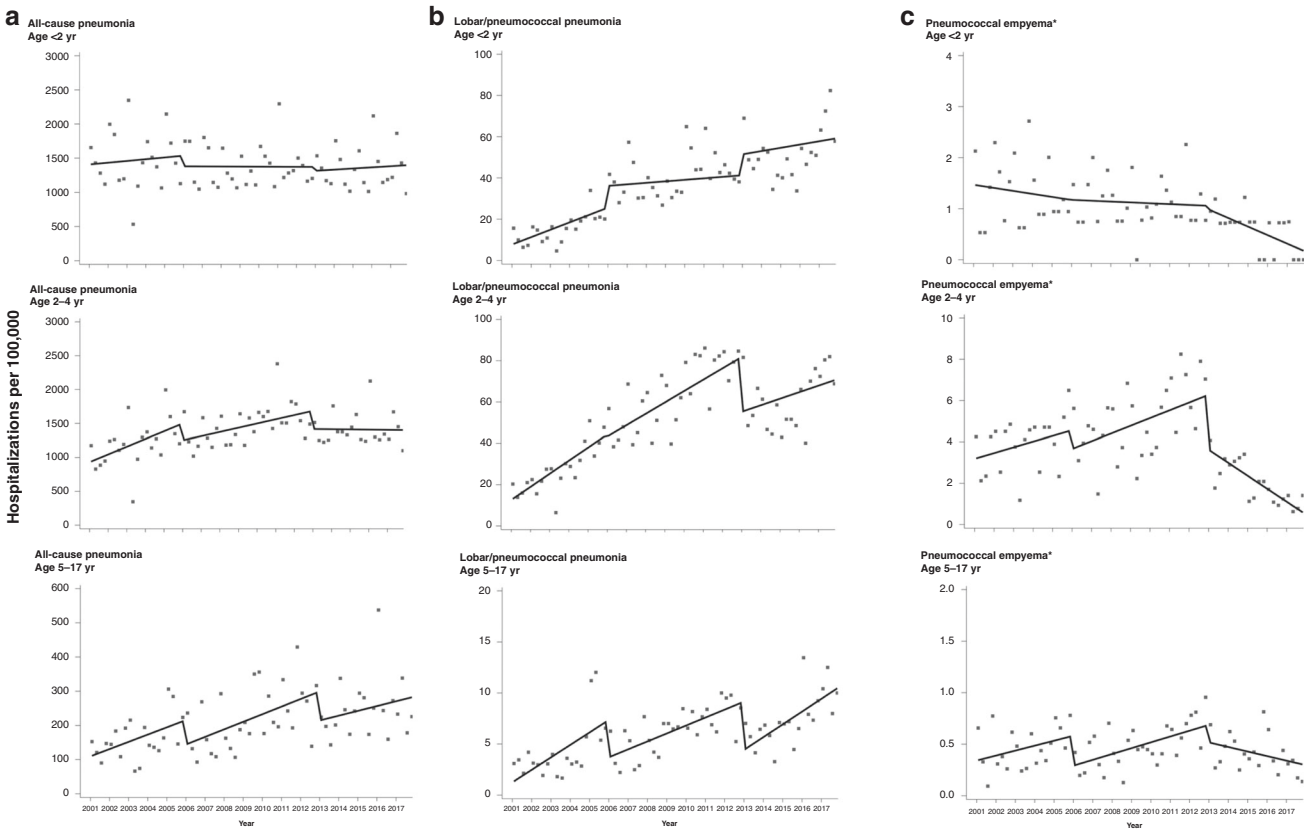

Fig. 3 Age-specific time series analysis of childhood pneumonia in the study period. The impact of pneumococcal conjugate vaccines on the seasonal incidence rates of (**a**) all-cause pneumonia, (**b**) lobar/pneumococcal pneumonia, and (**c**) pneumococcal empyema in children aged <2, 2–4, and 5–17 years by the interrupted time series with a segmented regression model. *Pneumococcal pneumonia with parapneumonic pleural effusion was also included in the analyses.

The increasing trend of lobar/PnC pneumonia in the last 2 years (2016–2017) may implicate increased carriage of less invasive non-vaccine serotypes. By surveillance of culture-confirmed PnC disease in Taiwan, PCV13 additional serotypes in the clinical isolates decreased from 52.0% in 2012 to 21.7% in 2015, but increased slightly to 26.7% because of serotype 19A in 2016.[27] The non-vaccine serotypes (mainly 15A, 15B/C, 23A) increased significantly from 18.4% in 2012 to 66.7% in 2016.[27] The non-vaccine serotypes majorly contributed to non-IPD cases, defined as isolation of *S. pneumoniae* from nonsterile sites, with a slight but not significant increase of PnC disease admission rate (per 10,000) from 13.2 in 2012 to 18.0 in 2016.[27] The serotype replacement, through a capsular switch and clonal expansion, reflected massive selection pressure exerted on the PnC ecology by the vaccines and antimicrobials.[4,28] The emergence of highly resistant non-vaccine serotype 15B/C has also been reported.[28] Another nasopharyngeal carriage study in Taiwan in 2016–2018 showed that the PnC carriage rate was 20.2% in healthy children and 24.0% in children with otitis media.[29] Non-vaccine serotypes accounted for the majority of the isolates (90.9% and 71.4%, respectively). Serotype 19A remained the second most common serotype (25%) in children with otitis media despite high PCV13 coverage. Therefore, residual serotype 19A and emerging non-vaccine serotypes may be associated with the upsurge of lobar/PnC pneumonia in this period.

The unique vaccination strategy in Taiwan (catch-ups before the primary infant series) may have an association with the significant increase of PnC pneumonia in 2016–2017. A nationwide study by Taiwan Centers for Disease Control showed vaccine effectiveness was 81% (69–88%) within 6 months of the last dose of PCV, but declined to 19% (−21 to 45%) after 2 years.[7] Another study in Taiwan also concluded children receiving the toddler catch-up PCV13 had a lower risk to develop vaccine-type invasive PnC pneumonia than children on a primary infant schedule.[30] With the toddler PCV13 catch-ups gradually replaced by the PCV13 infant schedule, the birth cohorts received their last dose of PCV13 earlier in life. The waning immunity from the infant schedule (booster dose at 12–15 months) could create an immunological "window" in children aged > 3 years. The local epidemiology pinpointed children aged 2–4 years were at higher risk to develop severe pneumonia before and after PCV introduction.[5,9,10] The changing dynamics of immunity could have an impact on the increase of PnC disease. Nevertheless, the increased PnC pneumonia cases were associated with less need for intensive care or invasive procedures in the post-PCV13 era. A recent study also confirmed PnC serotype-specific immunoglobulin G could persist above 0.35 μg/ml longer (≥5 years) in children with catch-up (1–2 doses) than children with 2 + 1 or 3 + 1 immunization.[31] These findings, however, implicated not only PCV13-induced immune memory but also natural boosting from residual diseases and colonization. The study also showed a low but stable carriage rate (5–7%) of serotype 19A and an increase of non-vaccine serotypes in 2014–2017.[31] The national PCV13 program significantly reduced overall IPD, especially serotype 19A, in children aged < 5 years[12] and severe pneumonia as indicated in our study. The rebound of PnC pneumonia may be related to carriage acquisition of residual vaccine serotypes and emerging non-vaccine serotypes.[11,31]

Our study has several limitations. First, the coded diagnoses may not represent true cases. Nevertheless, we evaluated the verification cohort with a good positive predicted value. The proportion of lobar/PnC pneumonia and parapneumonic diseases among all-cause pneumonia remained comparable in the study period. We used all diagnoses for analysis instead of only the

Table 2. Incidence rates and ratios of pneumococcal pneumonia outcomes before and after PCV13 national immunization program.

Age (years)	2011–2012	2014–2015	2016–2017	IRR 2014–2015/2011–2012	IRR 2016–2017/2014–2015	IRR 2016–2017/2011–2012
Lobar/pneumococcal pneumonia						
<2	181.7	173.7	239.5	0.96 (0.89–1.03)	1.38 (1.29–1.48)	1.32 (1.23–1.41)
2–4	311.8	202.6	277.9	0.65 (0.62–0.68)	1.37 (1.30–1.44)	0.89 (0.85–0.93)
5–17	32.2	24.1	39.4	0.75 (0.70–0.80)	1.64 (1.53–1.75)	1.22 (1.15–1.30)
Pneumococcal empyema[a]						
<2	3.9	1.7	0.6	0.44 (0.23–0.83)	0.36 (0.13–0.99)	0.16 (0.06–0.40)
2–4	26.2	9.5	4.6	0.36 (0.29–0.45)	0.48 (0.35–0.66)	0.18 (0.13–0.23)
5–17	2.6	1.8	1.3	0.70 (0.55–0.88)	0.70 (0.53–0.94)	0.49 (0.38–0.64)

The average incidence rates in respective periods are per 100,000. The numbers within the parentheses denote 95% confidence intervals of the IRRs.
IRR incidence rate ratio, *PCV* pneumococcal conjugate vaccine.
[a]Pneumococcal pneumonia with parapneumonic pleural effusion was also included in the analyses.

Table 3. The disease burden of childhood pneumonia after universal PCV13 vaccination in 2013–2017 as compared with 2006–2012 (reference) by the logistic regression model with the adjustment of age, sex, area, and season.

	Lower respiratory tract infection[a]			Lobar/pneumococcal pneumonia			Pneumococcal empyema		
Age (years)	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Intensive care									
0–17	0.86	0.83–0.88	<0.0001	0.58	0.53–0.63	<0.0001	0.55	0.38–0.81	0.002
<2	0.78	0.75–0.81	<0.0001	0.59	0.49–0.71	<0.0001	1.63	0.29–9.12	0.58
2–4	0.91	0.87–0.96	0.0003	0.55	0.48–0.63	<0.0001	0.47	0.28–0.77	0.003
5–17	0.91	0.87–0.95	<0.0001	0.62	0.52–0.73	<0.0001	0.58	0.30–1.13	0.14
Mechanical ventilation									
0–17	0.72	0.68–0.76	<0.0001	0.51	0.41–0.62	<0.0001	0.73	0.47–1.14	0.16
<2	0.60	0.55–0.66	<0.0001	0.45	0.30–0.69	0.0002	3.80	0.94–15.41	0.062
2–4	0.79	0.70–0.89	<0.0001	0.47	0.34–0.64	<0.0001	0.60	0.33–1.08	0.09
5–17	0.78	0.73–0.85	<0.0001	0.60	0.42–0.86	0.006	0.60	0.22–1.60	0.30
Surgical procedures									
0–17	0.66	0.60–0.73	<0.0001	0.42	0.36–0.49	<0.0001	0.57	0.38–0.87	0.009
<2	0.62	0.48–0.81	0.0003	0.22	0.13–0.40	<0.0001	0.62	0.12–3.13	0.57
2–4	0.50	0.41–0.60	<0.0001	0.39	0.32–0.48	<0.0001	0.57	0.32–1.00	0.05
5–17	0.78	0.68–0.89	0.0002	0.57	0.43–0.75	<0.0001	0.60	0.29–1.25	0.17
In-hospital death									
0–17	0.61	0.54–0.69	<0.0001	0.46	0.26–0.81	0.007	NA		
<2	0.56	0.44–0.70	<0.0001	0.19	0.02–1.58	0.124	NA		
2–4	0.69	0.51–0.93	0.013	0.39	0.17–0.89	0.026	NA		
5–17	0.61	0.52–0.72	<0.0001	0.68	0.29–1.58	0.37	NA		

OR odds ratio, *CI* confidence interval, *NA* not available due to limited numbers of fatal cases in pneumococcal empyema.
[a]Lower respiratory tract infection was defined as all-cause pneumonia except for lobar/pneumococcal pneumonia.

first-listed diagnosis. The trend, however, was similar. Second, we did not identify children with underlying medical conditions, who were at greater risks for developing PnC diseases. The uptake rates of the public-funded PCV program for the high-risk population since 2009 was unknown. The vaccination records could not be traced in the NHI Research Database. Third, the standards of care varied across the hospitals and the study period. The impact of PCVs could not be adjusted for other factors, such as breastfeeding, indoor air pollution, socioeconomic status, or the magnitude of other vaccination programs.[6]

In conclusion, the PCV13 national immunization program at high uptake rates had a substantial impact on reducing severe childhood pneumonia, not only in the targeted population but also with a significant herd effect. The intensive/invasive medical needs and in-hospital death of LRTIs also decreased as a part of the long-term impact. After the early decline, we observed an increase in lobar/PnC pneumonia cases. Continued surveillance of PnC diseases and their serotypes is important for further prevention and management.

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AUTHOR CONTRIBUTIONS

J.-T.L., J.-W.L., and C.-Y.W. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. H.-M.C. collected data, carried out the initial analyses, and reviewed the manuscript. C.-Y.L., L.-Y.C., and L.-M.H. conceptualized and designed the study and critically reviewed and revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

INFORMED CONSENT

The patient consent was not required.

ADDITIONAL INFORMATION

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