



National surveillance of invasive pneumococcal diseases in Taiwan, 2008–2012: Differential temporal emergence of serotype 19A[☆]



Chuen-Sheue Chiang^{a,b,*}, Ying-Yan Chen^a, Shr-Fong Jiang^a, Ding-Ping Liu^a,
Pei-Hsiu Kao^a, Hwa-Jen Teng^a, Tsung-Lin Kuo^a, Shu-Man Yao^a, Lei-Ron Tseng^a,
Yu-Lan Wang^a, Ho-Sheng Wu^a, Feng-Yee Chang^{a,c}, Tzou-Yien Lin^{d,e,**}

^a Centers for Disease Control, Taipei, Taiwan

^b Center of General Education, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan

^c Department of Internal Medicine, National Defense Medical Center, Taipei, Taiwan

^d Ministry of Health and Welfare, Taipei, Taiwan

^e Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taoyuan, Taiwan

ARTICLE INFO

Article history:

Received 21 November 2013

Received in revised form 4 April 2014

Accepted 21 April 2014

Available online 29 April 2014

Keywords:

Invasive pneumococcal disease

National surveillance

Streptococcus pneumoniae

Serotype 19A

Taiwan

ABSTRACT

Introduction: Serotype replacement after the introduction of seven-valent pneumococcal conjugate vaccine (PCV7) and the future availability of multivalent PCVs prompted the listing of invasive pneumococcal disease (IPD) as a notifiable disease in Taiwan in October 2007. Here, we report the national surveillance results.

Methods: The study population comprised the whole nation of Taiwan from 2008 to 2012. Restricting to cases with viable isolates, we calculated the incidence, case fatality ratio, prevalence of serotype 19A, and percentage of vaccine preventable IPD.

Results: 3659 cases of IPD were identified yielding an incidence of 3.2 per 100,000 population; the highest incidence was among children aged 2–4 years (21.1 per 100,000 population). The case fatality ratio was 9.2% and the highest ratio was among adults aged ≥ 75 years (19.0%). The percentage of PCV7 preventable IPD decreased for all age groups, especially sharply among children aged 2–4 years, from 65.8% in 2008 to 12.9% in 2012. The prevalence of serotype 19A increased from 5.5% in 2008 to 25.3% in 2012 among all *Streptococcus pneumoniae*, displaying a differential temporal emergence among different age groups. Serotype 19A became the most prevalent serotype among children aged < 2 years in 2009, children aged 2–4 and 5–17 years in 2010, and adults aged 18–49 years in 2012.

Conclusions: The incidence of IPD fluctuated during the study period, with ongoing decrease due to PCV7 vaccine serotypes and increase due to non-vaccine serotypes. Serotype 19A became the most prevalent serotype in 2010 among all *S. pneumoniae*.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Streptococcus pneumoniae (pneumococcus) is the leading cause of serious infection worldwide, and was estimated to be the cause

for 476,000 of the 8.8 million annual global deaths among children < 5 years of age in 2008 [1]. Invasive pneumococcal disease (IPD), defined as *S. pneumoniae* invading normally sterile body sites [2], places young children and the elderly at particularly high risk.

The capsular polysaccharides on the surface of *S. pneumoniae* form the basis for serotype classification of the bacterium into more than 90 serotypes [3] and for vaccine development. Four vaccines have been available for the prevention of *S. pneumoniae* infection. They are, in order of introduction, the 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 7-, 10-, and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13, respectively). Vaccination with PPV has been shown to reduce the risk of IPD in elderly individuals [4]. Widespread immunization of children with PCV7 decreased IPD rates for vaccinated children [5–11] as well as for unvaccinated age groups, due to “herd

[☆] The contents are prepared by the authors and do not necessarily represent the official views of the Centers for Disease Control, Taiwan.

* Corresponding author at: Center for Research, Diagnostics, and Vaccine Development, Centers for Disease Control, No. 161, Kun-Yang Street, Taipei, Taiwan. Tel.: +886 2 26531350; fax: +886 2 27885075.

** Corresponding author at: Ministry of Health and Welfare, 5F, No. 36, Tacheng Street, Datong District, Taipei 10341, Taiwan. Tel.: +886 2 85906511; fax: +886 2 85906051.

E-mail addresses: cschiang10@cdc.gov.tw (C.-S. Chiang), alinpid@gmail.com (T.-Y. Lin).

immunity" [5,8,11]. However, serotype replacement, an increase in non-vaccine serotypes among asymptomatic carriers and causes of IPD, was also frequently reported after PCV7 vaccination [5,12] and compromised the effectiveness of vaccination.

In Taiwan, PPV23, PCV7, PCV10, and PCV13 were approved in January 2001, October 2005, April 2010, and April 2011, respectively, and have been available in the private sector since then. However, no national immunization program has been implemented. Due to the potential for serotype replacement and future availability of various multivalent PCVs, IPD was listed as a notifiable disease in Taiwan in October 2007, so that incidences, circulating serotypes, antimicrobial susceptibility, and the impact of interventions could be monitored. It is mandatory to report IPD cases within 7 days of establishing the clinical diagnosis and to deliver the isolated *S. pneumoniae* to the Centers for Disease Control, Taiwan (TCDC). Here, we report the national surveillance results from 2008 to 2012, including the incidence, case fatality ratio, serotypes, and percentage of vaccine-preventable cases.

2. Methods

2.1. Case definition, data and invasive *S. pneumoniae* isolate collection

A case of IPD was defined as isolation of *S. pneumoniae* from a normally sterile body site, such as blood or cerebrospinal fluid (CSF). Since October 2007, every hospital in Taiwan has been required to report IPD cases of all ages and to send *S. pneumoniae* isolates to the TCDC. In general practice in Taiwan, a blood culture is taken for cases of suspected pneumonia/lower respiratory tract infection before antibiotic prescription, and a lumbar puncture is performed for cases of meningitis as early as possible. Infection control personnel in each hospital monitor report from the microbiology laboratory for isolation of *S. pneumoniae* from specimens originating from either sterile body sites or patients in intensive care units. When a report is detected, the patient's attending physician is consulted regarding whether it is an IPD case. Once confirmed, the physician is urged to authorize infection control personnel to complete a notification form in the National Notifiable Disease Surveillance System of the TCDC over the Internet. During the process of notification, demographic information about each IPD patient is provided by the reporting hospitals, including gender, age, date of disease onset. Staff in the microbiology laboratory prepare the isolated *S. pneumoniae* in transport medium (Amies charcoal-single plastic swab, COPAN Italia, Italy), and infection control personnel then mail it to the TCDC. The body site of isolation is indicated along with the bacterial isolate. Because infection control personnel scrutinize all reports from the microbiology laboratory daily, notification is expected to be more complete, reducing the possibility of cases being overlooked by clinicians or the laboratory. From 2008–2009 and 2010–2012, 98.8% and 100%, respectively, of notified IPD cases were accompanied by an *S. pneumoniae* shipment from the reporting hospitals.

IPD cases with disease onset between 1 January 2008 and 31 December 2012 were collected for analysis in this study. The population of Taiwan was approximately 23.1 million individuals. The IPD incidence (cases per 100,000 population) was calculated using the case numbers and the mid-year population estimates provided by the Ministry of Internal Affairs [13]. The case fatality ratio was calculated by dividing fatal cases by all cases in a given age group.

2.2. Serotyping of *S. pneumoniae*

Upon receipt, *S. pneumoniae* isolates were subcultured immediately and confirmed by standard microbiological methods,

followed by serotyping using the capsular swelling method (Quellung reaction) with antisera obtained from the Statens Serum Institut (Copenhagen, Denmark) according to the procedure provided by the manufacturer. The serotype was determined for most *S. pneumoniae* isolates within two weeks after IPD onset.

2.3. Statistical analysis

All statistical analyses were performed using the chi-square test and the two-tailed Fisher's exact test if the expected cell value for any observation was ≤ 5 . A p value < 0.05 was considered statistically significant.

3. Results

3.1. Case number and body sites of *S. pneumoniae* isolation

From 1 January 2008 through 31 December 2012, a total of 3813 IPD cases were reported to the TCDC; 3659 *S. pneumoniae* isolates were confirmed and further serotyped (96.0% in total, ranging from 95.4% to 97.0% for an individual year). Most excluded cases were due to an absence of viable *S. pneumoniae* from the received bacterial swabs. All analysis was based on the 3659 confirmed and serotyped cases, originating from 160 hospitals distributed across Taiwan. *S. pneumoniae* was isolated from blood in 91.3% of patients, from pleural fluid in 5.1% of patients, from CSF in 2.5% of patients, from peritoneal fluid in 0.5% of patients, from synovial fluid in 0.4% of patients, and from other sterile body sites in 1.1% of patients. The ratio of male to female patients was 1.9.

3.2. Incidence and case fatality ratio

The patients ranged in age from 2 months to 106 years, with 23.6% and 20.7% of all cases occurring among children (< 5 years old) and the elderly (≥ 75 years old), respectively (Table 1). The overall incidence was 3.2 cases per 100,000 population. By age group, the highest incidence was 21.1 cases per 100,000 population among children aged 2–4 years, followed by 14.0 cases per 100,000 population among adults aged ≥ 75 years. The incidence fluctuated by year between 2.9 cases per 100,000 population in 2009 and 3.4 cases per 100,000 population in 2011. The overall case fatality ratio was 9.2%, and the highest rate, 19.0%, was found among adults aged ≥ 75 years (Table 1). The case fatality ratio was significantly different from previous year for all age in 2011, and age group 50–64 years in 2009 and 2011.

3.3. Serotypes of *S. pneumoniae* and a differential temporal emergence of serotype 19A

With the exception of 16 non-typeable *S. pneumoniae* isolates, 53 serotypes were identified. The most prevalent 12 serotypes were 14 (16.3%), 19A (14.9%), 3 (12.8%), 23F (11.7%), 19F (8.6%), 6B (8.5%), 23A (3.5%), 6A (3.5%), 15B (2.0%), 9V (1.9%), 4 (1.9%), 10A (1.4%), accounting for 87.0% of all isolates. Twenty-eight isolates (0.8%) were serotype 18C. Serotypes 2, 5, and 33F, included in PCV13 and/or PPV23, were not detected. The temporal trend of these major serotypes was shown (Fig. 1).

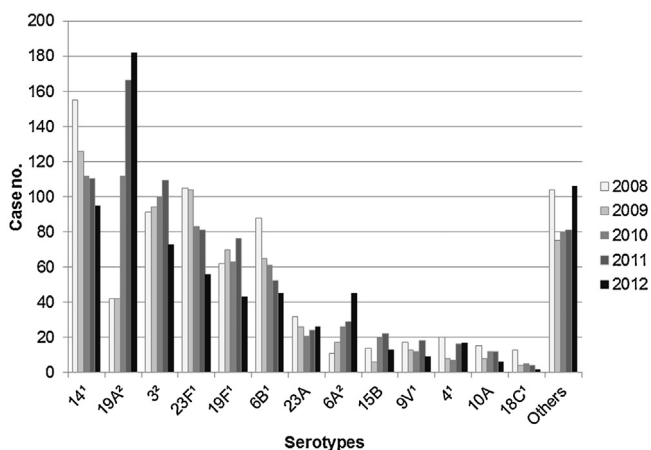
The proportion of serotype 19A among all *S. pneumoniae* isolates increased from 5.5% in 2008 to 25.3% in 2012 (Table 2, $p < 0.001$), becoming the most prevalent serotype in 2010. Rather than emerging simultaneously among all age groups, however, serotype 19A appeared prevalently first in the very young and then progressed to the elderly. As a result, serotype 19A became the most prevalent serotype among children < 2 years in 2009 ($p < 0.05$), among children aged 2–4 and 5–17 years in 2010 ($p < 0.001$ and $p < 0.05$, respectively), and among adults aged 18–49 years in 2012

Table 1Case number, incidence, and case fatality ratio of invasive pneumococcal disease by age group and year, Taiwan, 2008–2012 ($n = 3659$).

Age	Case number (incidence, cases per 100,000 population)/case fatality ratio (%)					2008–2012
	2008	2009	2010	2011	2012	
<2 years	51 (12.9)/2.0	44 (11.4)/2.3	44 (12.0)/2.3	45 (12.7)/4.4	32 (8.2)/6.3	216 (11.4)/3.2
2–4 years	114 (17.7)/2.6	96 (15.3)/2.1	152 ^b (24.7)/2.0	154 (25.4)/3.2	132 (22.7)/2.3	648 (21.1)/2.5
5–17 years	35 (0.9)/0.0	39 (1.0)/0.0	48 (1.3)/2.1	47 (1.3)/2.1	58 (1.7)/1.7	227 (1.2)/1.3
18–49 years	151 (1.3)/7.3	124 (1.1)/7.3	117 (1.0)/8.5	133 (1.1)/10.5	106 (0.9)/4.7	631 (1.1)/7.8
50–64 years	115 (3.0)/13.9	130 (3.2)/5.4 ^a	121 (2.8)/6.6	163 ^a (3.6)/15.3 ^a	145 (3.1)/10.3	674 (3.2)/10.5
65–74 years	126 (9.3)/8.7	80 ^b (5.8)/5.0	110 ^a (7.9)/8.2	96 (6.9)/12.5	92 (6.5)/13.0	504 (7.3)/9.5
≥75 years	177 (17.5)/18.6	145 ^a (13.8)/19.3	122 (11.3)/13.9	162 ^a (14.5)/21.0	153 (13.3)/20.9	759 (14.0)/19.0
All age	769 (3.3)/9.8	658 ^a (2.9)/7.8	714 (3.1)/6.9	800 ^a (3.4)/11.6 ^a	718 ^a (3.1)/9.7	3659 (3.2)/9.2

^a $p < 0.05$ compared to previous year.^b $p < 0.001$ compared to previous year.**Table 2**Differential temporal emergence of *Streptococcus pneumoniae* serotype 19A by age group and year, Taiwan, 2008–2012 ($n = 3659$).

Age	2008 % (rank) ^a	2009 % (rank)	2010 % (rank)	2011 % (rank)	2012 % (rank)
<2 years	5.9 (5)	25.0 (1)^b	29.5 (1)^b	42.2 (1)^c	40.6 (1)^c
2–4 years	16.7 (4)	18.8 (3)	40.8 (1)^c	53.9 (1)^c	66.7 (1)^c
5–17 years	5.7 (6)	10.3 (3)	22.9 (1)^b	48.9 (1)^c	44.8 (1)^c
18–49 years	2.6 (10)	4.8 (6)	6.0 (5)	12.8 (3)^b	15.1 (1)^c
50–64 years	3.5 (7)	2.3 (7)	5.8 (6)	9.2 (5)	13.1 (2)^b
65–74 years	3.2 (7)	0 (20)	10.0 (4)	2.1 (10)	7.6 (5)
≥75 years	3.4 (6)	0 (22)	0.8 (15)	4.3 (8)	8.5 (3)^b
All age	5.5 (6)	6.4 (6)	15.7 (1)^c	20.8 (1)^c	25.3 (1)^c

^a Proportion (%) and rank of serotype 19A among *Streptococcus pneumoniae* isolates.^b $p < 0.05$ compared to 2008.^c $p < 0.001$ compared to 2008.**Fig. 1.** Trends of the 12 most prevalent serotypes, ranging from 598 to 53 *S. pneumoniae* strains, plus serotype 18C (28 strains), in 2008–2012. These 13 serotypes consist of 87.8% of all *S. pneumoniae* strains. ¹ Serotypes included in PCV7; ² extra serotypes included in PCV13.

($p < 0.001$). Serotype 19A was the second, fifth, and third most prevalent serotype in 2012 among adults aged 50–64, 65–74, and ≥75 years, respectively ($p < 0.05$, $p = 0.14$, and $p < 0.05$).

3.4. Percentage of vaccine preventable IPD

The percentage of PCV7 preventable IPD decreased from 59.8% in 2008 to 37.2% in 2012 (Table 3, $p < 0.001$). This decrease was first observed among young children and was eventually significant for all age groups in 2012 ($p < 0.05$) compared to percentages in 2008, with the exception of adults aged 65–74 years ($p = 0.35$). The most dramatic decrease was observed among children aged 2–4 years (65.8% in 2008 to 12.9% in 2012, $p < 0.001$), followed by children <2 years ($p < 0.001$) and children aged 5–17 years ($p < 0.05$). The percentage of PCV13 preventable IPD was higher among children than

among adults, and a slight decrease was observed among children in 2012. The percentage of PPV23 preventable IPD was approximately 80–90% for all age groups in 2008–2011 and declined slightly in 2012. The percentage of PCV10 preventable IPD (data not shown) was almost identical to that of PCV7 because only 2 serotype 1 and 10 serotype 7F isolates of *S. pneumoniae* were identified.

4. Discussion

We present data from the first five years of national surveillance of IPD in Taiwan. With mandatory case reporting and *S. pneumoniae* isolate collection, 96% of all notified IPD cases had viable *S. pneumoniae* isolates for serotyping. Many countries have national surveillance systems for IPD; however, collection of *S. pneumoniae* is mostly voluntary [14]. In England and Wales, the national surveillance system was created in 1996, and 81% of *S. pneumoniae* isolates from culture-positive IPDs were serotyped from 2009 to 2010 [5]. In Denmark, serotyping of *S. pneumoniae* isolates has been performed since 1937, and more than 90% of all IPD isolates were estimated to be included in the national laboratory surveillance system in recent years [11].

The incidence of IPD in our study (3.2 cases per 100,000 population) is higher than previously reported [15]. Most IPD patients in Taiwan are admitted to hospitals where case reporting and *S. pneumoniae* collection is mandatory. Therefore, we believe that the number of IPD cases that were not detected or reported was small and that the incidence calculated in the current study is close to the true incidence in Taiwan. The incidence in our study is lower than that previously reported for many other countries [5,7,8,11], either ranging from 15.0 to 24.4 cases per 100,000 population before the introduction of PCV7, or ranging from 10.6 to 17.1 cases per 100,000 population 1 to 7 years after the national, widespread introduction of PCV7.

No significant decline in IPD incidence was observed in our study, including among children <2 years or aged 2–4 years. This

Table 3Percentage of vaccine preventable invasive pneumococcal disease by age group and year, Taiwan, 2008–2012 ($n = 3659$).

Age	PCV7 ^a					PCV13 ^b					PPV23 ^c				
	2008	2009	2010	2011	2012	2008	2009	2010	2011	2012	2008	2009	2010	2011	2012
<2 years	78.4	63.6	47.7^e	31.1^e	28.1^e	86.3	93.2	84.1	84.4	81.3	92.2	88.6	84.1	82.2	75.0^d
2–4 years	65.8	69.8	46.1^d	33.8^e	12.9^e	92.1	94.8	95.4	94.2	86.4	89.5	91.7	89.5	90.3	82.6
5–17 years	57.1	76.9	47.9	34.0^d	27.6^d	77.1	94.9	81.3	91.5	82.8	80.0	92.3	85.4	93.6	82.8
18–49 years	55.0	50.8	45.3	45.1	39.6^d	70.9	78.2	75.2	75.9	74.5	79.5	83.1	81.2	85.0	77.4
50–64 years	59.1	53.1	52.9	49.1	44.8^d	77.4	79.2	78.5	82.8	77.9	87.0	83.1	87.6	84.0	77.2^d
65–74 years	53.2	56.3	46.4	54.2	46.7	77.8	76.3	78.2	80.2	76.1	86.5	78.8	89.1	85.4	80.4
≥75 years	60.5	60.7	50.0	51.2	49.0^d	78.0	80.0	76.2	75.9	77.8	86.4	89.0	86.1	82.1	77.8^d
All age	59.8	59.3	48.0^e	44.6^e	37.2^e	79.1	83.0	81.7	82.8	79.2	85.7	86.0	86.6	85.6	79.1^e

^a PCV7 (7-valent pneumococcal conjugate vaccine): 4, 6B, 9V, 14, 18C, 19F and 23F.^b PCV13: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.^c PPV23: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F.^d $p < 0.05$ compared to 2008.^e $p < 0.001$ compared to 2008.

result is attributable to the combination of a decrease in IPD due to serotypes included in PCV7 and an increase in IPD due to serotypes not included in PCV7. In Taiwan, PCV7, PCV10, and PCV13 have been available at parent's expense since they were approved. Only after July 2009, the government began to provide free PCV7, followed by PCV10 or PCV13 when available, to children <5 years who were either at risk of severe disease or financially disadvantaged. In a previous report, the cumulative coverage rate of PCV7 among children aged <5 years was 0.7% in 2005, 8.6% in 2006, 15.9% in 2007 and 25.2% in 2008 based on the manufacture's estimate [16]. In another study for nasopharyngeal carriage of *S. pneumoniae*, the coverage rate of PCV7 vaccination (received at least one dose of PCV7) was 0.2% in 2005, 5.7% in 2006, 17.1% in 2007, 26.9% in 2008, 37.5% in 2009 and 45.5% in 2010 among the 9705 child participants <5 years of age [17]. Although pneumococcal vaccination has not been implemented nationwide in Taiwan, partial vaccination coverage has contributed, at least in part, to the observed decline in IPD due to serotypes included in PCV7.

The highest incidence was among children aged 2–4 years, consistent with an earlier report from Taiwan [15], but in contrast to many reports from other countries, where the highest incidence was recorded among children <2 years [5,6,10]. This discrepancy may be attributable to many factors, including attendance at day care centers, which was reported to be strongly associated with IPD [18,19] and pneumococcal carriage [17] in children. In Taiwan, most children <2 years are cared for by relatives or nannies at either the children's or care takers' homes. Therefore, the lack of exposure to large groups of children at day care centers likely contributed substantially to the lower IPD incidence among children <2 years. To our knowledge, the only other study that documented that the highest incidence was among children aged 2–4 years was from Singapore in 2005–2010 [20]. Similar to Taiwan, the majority of infants in Singapore are looked after at home or in small home-care centers. Another possible factor that would need further investigation is that the higher rate among children aged 2–4 years may just be reflecting impact of the vaccination among children <2 years since 2005.

An increase in the prevalence of *S. pneumoniae* serotype 19A has been observed in many countries after the introduction of PCV7 [5,6,8,21]. However, to our knowledge, our observation of the differential temporal emergence of serotype 19A among different age groups, although somewhat expected, has never been reported. This differential temporal emergence was likely due to vaccination pressure among young children, and thus, children were the first age group to be affected. When vaccination coverage among young children increased over time, herd immunity spread to the older age groups who were not vaccinated, and the prevalence of serotype 19A also increased in the latter age groups. The high rate

of antimicrobial resistance of serotype 19A [22] did not seem to play an important role in this differential temporal emergence; if it did, serotype 19A would be expected to emerge at the same time for all age groups. In the US and in England and Wales, IPD due to serotype 19A increased more than 3- and 2-fold [5,21], respectively, for all age groups four years after nationwide vaccination with PCV7 began. Without nationwide immunization with PCV7 in Taiwan, the rapid increase in serotype 19A was somewhat unexpected. It would be interesting to further characterize *S. pneumoniae* to reveal any clonal expansion or unique characteristics.

In our study, the reduction in IPD caused by serotypes 14, 23F and 6B was obvious, but no reduction was observed in serotype 19F. This finding raised concerns because serotype 19F was the fifth most prevalent serotype from IPD patients, and it was the most common serotype isolated from nasopharyngeal swabs among children <5 years in Taiwan [15,23]. A similar lack of reduction in serotype 19F was observed among children <5 years in Hong Kong [24] and among children between 2 and 5 years in Denmark [11] after vaccination with PCV7. In addition, we did not see an increase in the incidence of serotypes 6C, 7F, 22F, or 35, as has previously been reported [5,12,25].

The percentage of PCV7 preventable IPD among children <5 years declined sharply, clearly indicating that this vaccine is likely not enough to target residual disease among this age group in Taiwan. Neither is PCV10, as only 12 additional cases were preventable. Apparently, the recently introduced PCV13 is the best choice available, as more than 80% of IPD cases were preventable. Therefore, based on this study, the government began to provide only PCV13 for immunization to those children eligible for free vaccine since October 2011. However, a decrease in the percentage of PCV13 preventable IPD among children <2 years and 2–4 years in 2012 was observed, likely attributable to partial vaccination coverage by PCV13. Therefore, close monitoring of the serotypes of future *S. pneumoniae* isolates is essential to further determine the impact of PCV13 vaccination.

Another interesting observation from this study is that the highest number of IPD cases ($n = 800$) and the highest annual fatality rate (11.6%) occurred in 2011, coinciding with the post-pandemic circulation period of influenza A(H1N1) in Taiwan. During this time, a sharp increase in hospitalized and fatal cases due to influenza A(H1N1) was recorded, as well as an age shift in fatal cases to older adults aged 50–64 years [26,27]. Compared to 2010, the increase in IPD cases as well as case fatality ratio was significant among adults aged 50–64 in 2011 (Table 1; 163 vs. 121, and 15.3% vs. 6.6%, respectively). Adults aged 50–64 years appeared to be the most affected age group in both scenarios, and *S. pneumoniae* was the most prevalent bacterial pathogen associated with fatal cases in the 2009 influenza A(H1N1) pandemic in the United States [28].

Nevertheless, further investigation is needed to confirm any correlation between post-pandemic circulation of influenza A(H1N1) and IPD in Taiwan in 2011.

In conclusion, we presented data from the first five years of national surveillance of IPD in Taiwan. The results provide timely information for IPD epidemiology and vaccination policy. To further assess disease severity and vaccination effectiveness, medical record and immunization information for individual patients needs to be reviewed and obtained through the hospitals and the National Immunization Information System, respectively. In addition, our system, based on infection control personnel, can be used to supplement existing surveillance systems in other countries that are based on physicians or laboratories to improve case reporting and *S. pneumoniae* collection.

Acknowledgements

We thank Dr. L. Kristopher Siu (National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli, Taiwan) for his comments on the manuscript. This work was supported by grants DOH98-DC-2004, DOH99-DC-2007, DOH99-DC-2008, DOH100-DC-2015, DOH101-DC-2202, DOH102-DC-2502, and DOH102-DC-2601 from the Centers for Disease Control, Taipei, Taiwan.

Authors' contributions: CSC, YYC, DPL, HSW, FYC, and TYL established the surveillance system. YYC, SFJ, TLK, SMY, LRT, and YLW were responsible for data collection. CSC, YYC, PHK, and HJT were responsible for data management and analysis. CSC, YYC, DPL, HSW, FYC, and TYL drafted the paper. All authors have approved the final version for submission. **Conflicts of interest:** TYL has received research funding from Pfizer and GlaxoSmithKline. CSC, YYC, SFJ, DPL, PHK, HJT, TLK, SMY, LRT, YLW, HSW, and FYC declare that they have no conflicts of interest. **Role of the funding source:** The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or report writing. The corresponding authors had full responsibility for the decision to submit for publication.

References

- [1] World Health Organization. Pneumococcal vaccines; WHO position paper – 2012. *Wkly Epidemiol Rec* 2012;87:129–44.
- [2] Randle E, Ninis N, Inwald D. Invasive pneumococcal disease. *Arch Dis Child Educ Pract Ed* 2011;96(5):183–90.
- [3] Calix JJ, Porambo RJ, Brady AM, Larson TR, Yother J, Abeygunwardana C, et al. Biochemical, genetic, and serological characterization of two capsule subtypes among *Streptococcus pneumoniae* serotype 20 strains: discovery of a new pneumococcal serotype. *J Biol Chem* 2012;287(33):27885–94.
- [4] Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med* 2003;348(18):1747–55.
- [5] Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis* 2011;11(10):760–8.
- [6] Tyrrell GJ, Lovgren M, Chui N, Minion J, Garg S, Kellner JD, et al. Serotypes and antimicrobial susceptibilities of invasive *Streptococcus pneumoniae* pre- and post-seven valent pneumococcal conjugate vaccine introduction in Alberta, Canada, 2000–2006. *Vaccine* 2009;27(27):3553–60.
- [7] Rodenburg GD, de Greeff SC, Jansen AG, de Melker HE, Schouls LM, Hak E, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. *Emerg Infect Dis* 2010;16(5):816–23.
- [8] Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010;201(1):32–41.
- [9] Vestreim DF, Lovoll O, Aaberge IS, Caugant DA, Hoiby EA, Bakke H, et al. Effectiveness of a 2 + 1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway. *Vaccine* 2008;26(26):3277–81.
- [10] Ruckinger S, van der Linden M, Reinert RR, von Kries R, Burckhardt F, Siedler A. Reduction in the incidence of invasive pneumococcal disease after general vaccination with 7-valent pneumococcal conjugate vaccine in Germany. *Vaccine* 2009;27(31):4136–41.
- [11] Harboe ZB, Valentiner-Branth P, Benfield TL, Christensen JJ, Andersen PH, Howitz M, et al. Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme. *Vaccine* 2010;28(14):2642–7.
- [12] Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. *J Infect Dis* 2007;196(9):1346–54.
- [13] <http://www.ris.gov.tw/zh-TW/346>
- [14] Pebody RG, Hellenbrand W, D'Ancona F, Ruutu P. Pneumococcal disease surveillance in Europe. *Euro Surveill* 2006;11(9):pii:646.
- [15] Hsieh YC, Lin PY, Chiu CH, Huang YC, Chang KY, Liao CH, et al. National survey of invasive pneumococcal diseases in Taiwan under partial PCV7 vaccination in 2007: emergence of serotype 19A with high invasive potential. *Vaccine* 2009;27(40):5513–8.
- [16] Liao WH, Lin SH, Lai CC, Tan CK, Liao CH, Huang YT, et al. Impact of pneumococcal vaccines on invasive pneumococcal disease in Taiwan. *Eur J Clin Microbiol Infect Dis* 2010;29(4):489–92.
- [17] Hsieh YC, Chiu CH, Chang KY, Huang YC, Chen CJ, Kuo CY, et al. The impact of the heptavalent pneumococcal conjugate vaccine on risk factors for *Streptococcus pneumoniae* carriage in children. *Pediatr Infect Dis J* 2012;31(9):e163–8.
- [18] Levine OS, Farley M, Harrison LH, Lefkowitz L, McGeer A, Schwartz B. Risk factors for invasive pneumococcal disease in children: a population-based case–control study in North America. *Pediatrics* 1999;103(3):E28.
- [19] Takala AK, Jero J, Kela E, Ronnberg PR, Koskeniemi E, Eskola J. Risk factors for primary invasive pneumococcal disease among children in Finland. *JAMA* 1995;273(11):859–64.
- [20] Thoon KC, Chong CY, Tee NW. Early impact of pneumococcal conjugate vaccine on invasive pneumococcal disease in Singapore children, 2005 through 2010. *Int J Infect Dis* 2012;16(3):e209–15.
- [21] Moore MR, Gertz Jr RE, Woodbury RL, Barkocy-Gallagher GA, Schaffner W, Lexau C, et al. Population snapshot of emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005. *J Infect Dis* 2008;197(7):1016–27.
- [22] Chen YY, Yao SM, Chen YH, Jiang SF, Kuo TL, Kao PH, et al. Antimicrobial susceptibility of invasive *Streptococcus pneumoniae* in Taiwan, 2008–2012. *Taiwan Epidemiol Bull* 2013;29(19):232–42.
- [23] Kuo CY, Hwang KP, Hsieh YC, Cheng CH, Huang FL, Shen YH, et al. Nasopharyngeal carriage of *Streptococcus pneumoniae* in Taiwan before and after the introduction of a conjugate vaccine. *Vaccine* 2011;29(32):5171–7.
- [24] Ho PL, Chiu SS, Ang I, Lau YL. Serotypes and antimicrobial susceptibilities of invasive *Streptococcus pneumoniae* before and after introduction of 7-valent pneumococcal conjugate vaccine, Hong Kong, 1995–2009. *Vaccine* 2011;29(17):3270–5.
- [25] Green MC, Mason EO, Kaplan SL, Lamberth LB, Stovall SH, Givner LB, et al. Increase in prevalence of *Streptococcus pneumoniae* serotype 6C at eight children's hospitals in the United States from 1993 to 2009. *J Clin Microbiol* 2011;49(6):2097–101.
- [26] Yang JR, Huang YP, Chang FY, Hsu LC, Lin YC, Su CH, et al. New variants and age shift to high fatality groups contribute to severe successive waves in the 2009 influenza pandemic in Taiwan. *PLoS ONE* 2011;6(11):e28288.
- [27] Chuang JH, Huang AS, Huang WT, Liu MT, Chou JH, Chang FY, et al. Nationwide surveillance of influenza during the pandemic (2009–10) and post-pandemic (2010–11) periods in Taiwan. *PLoS ONE* 2012;7(4):e36120.
- [28] Louie J, Jean C, Chen TH, Park S, Ueki R, Harper T, et al. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) – United States, May–August 2009. *Morb Mortal Wkly Rep* 2009;58(38):1071–4.